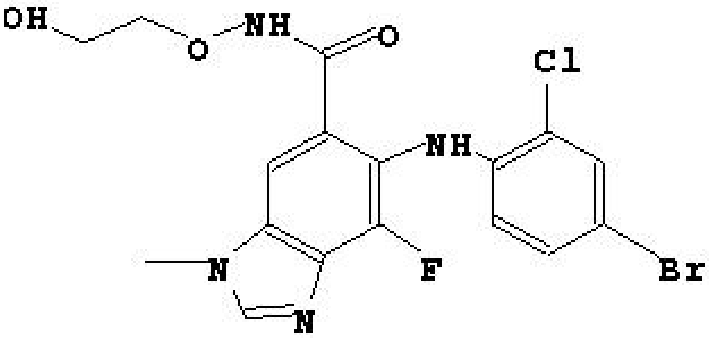
Adis Insight

Drug Profile

Selumetinib

Alternative Names: ARRY-142886; ARRY-886; AZD 142886; AZD-6244; AZD-6244 hydrogen sulfate; AZD6244 Hyd-Sulfate; AZD6244 hydrogen sulphate; NSC-748727; Selumetinib hydrogen sulfate

Latest Information Update: 15 Feb 2017



At a glance

Originator Array BioPharma

Developer Array BioPharma; AstraZeneca; Cancer Research UK; Merck & Co; National Cancer Centre (Singapore); National Cancer Institute (USA); Netherlands Cancer Institute; University Health Network; University of Cambridge; University of Liverpool

Class Antineoplastics; Benzimidazoles; Small molecules

Mechanism of Action MAP kinase kinase 1 inhibitors; MAP kinase kinase 2 inhibitors

Orphan Drug Status Yes - Thyroid cancer; Uveal melanoma

On Fast track No

New Molecular Entity Yes

Highest Development Phases

Phase III Thyroid cancer

Phase II Biliary cancer; Colorectal cancer; Neurofibromatoses; Non-small cell lung cancer

Phase I/II Astrocytoma; Glioma

Phase I Solid tumours

Preclinical Pancreatic cancer

Discontinued Acute myeloid leukaemia; Hepatocellular carcinoma; Malignant melanoma; Multiple myeloma; Uveal melanoma

Most Recent Events

01 Feb 2017 The National Cancer Institute plans a phase II trial for Pancreatic cancer (Late-stage disease, Metastatic disease, Monotherapy) in USA (PO) (NCT03040986)

20 Dec 2016 University of Texas M.D. Anderson Cancer Center plans a phase II trial for Non-small cell lung cancer (Combination therapy, Metastatic disease, Late-stage disease) in USA (NCT03004105)

17 Nov 2016 Discontinued - Phase-III for KRAS mutation-positive Non-small cell lung cancer (Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater) in Austria, Brazil, Canada, United Kingdom, Sweden, Italy, Israel, France, Australia, USA, Poland, Netherlands, Hungary, Germany, Spain, Romania, Belgium, Turkey, Chile, Argentina, Bulgaria, Portugal, Peru, Russia, Mexico, Ukraine (PO) because of unfavourable safety and efficacy results (before November 2016; AstraZeneca pipeline, November 2016)

Development Overview

Introduction

Selumetinib is an orally administered small molecule that inhibits MAP kinase kinase 1 and 2 (MEK1/2) in a selective, non-ATP-competitive fashion. This inhibition can prevent ERK activation, disrupt downstream signal transduction, and inhibit cancer cell proliferation and survival. Selumetinib has shown tumour suppressive activity in multiple rodent models of human cancer including melanoma, pancreatic, colon, lung and breast cancers. Array BioPharma undertook the initial development of this compound up to phase I. Phase III development is underway in the US, Brazil and the EU as a combination therapy for the treatment of patients with thyroid cancer and in phase II as a monotherapy for thyroid cancer in the US and Canada. Phase II development as a combination therapy is underway in colorectal cancer in the US. However, no development has been reported for the monotherapy of the drug in colorectal cancer in the US. Selumetinib is also being developed as a combination therapy in first-line treatment of patients with non-small cell lung cancer (NSCLC) in Canada and the UK. Phase II development is underway for the treatment of patients with biliary cancer in Canada. Phase II development for colorectal cancer and non-small cell lung cancer is ongoing in the Netherlands. Phase I/II development is underway for glioma and astrocytoma in the US. Development is in phase II for the treatment of patients with neurofibromatosis in the US and for biliary cancer in Japan. A phase I/II study is ongoing for the treatment of paediatric patients with neurofibromatosis in the US. Phase I development in combination with durvalumab is underway in the US for solid tumours. Preclinical development of selumetinib as combination therapy is ongoing in pancreatic cancer in the UK.

A fixed dose combination of selumetinib in combination with ipatasertib is being developed by Celator Pharmaceuticals, for the treatment of cancer [*see RDI profile* 800023960(Research programme fixed dose combination therapies Celator)].

AstraZeneca was conducting phase III development of selumetinib as a second-line, combination therapy for the treatment of patients with advanced KRAS mutation-positive NSCLC in the US, Canada, Europe, Australia, Israel and South America. However, development was terminated due to unfavourable safety and efficacy results.

Development for the treatment of uveal melanoma was discontinued after a pivotal trial failed to meet its primary endpoint.

AstraZeneca was collaborating with Merck on the development of a combination regimen comprising selumetinib and MK 2206 [*see RDI profile 800028810(MK 2206)*], for potential use in the treatment of solid tumours. MK 2206 inhibits AKT kinase and preclinical evidence indicated that the co-administration of these two compounds could enhance their anticancer properties. Furthermore, the simultaneous inhibition of two separate pathways that contribute to cancer growth could also have synergistic effects on slowing tumour cell growth. Phase I development is ongoing in the US and the UK, for this combination regimen.

Development of selumetinib as monotherapy for the treatment of pancreatic cancer appears to have been discontinued. AstraZeneca also discontinued development of selumetinib as a monotherapy and combination therapy for malignant melanoma. Other discontinued indications include acute myeloid leukaemia, hepatocellular carcinoma and multiple myeloma; these indications are not listed on the AstraZeneca company pipeline as of March 2015.

Company Agreements

AstraZeneca and the University of Cambridge and Cancer Research UK Cambridge Institute entered into a 2-year collaboration to advance cancer research by studying tumour mutations and evaluating investigational therapies in prostate, pancreatic and other cancers. The collaboration, signed in July

2013, will be focused on the use of tumour DNA, present in a patient's blood, to identify genetic biomarkers of their cancer and therefore the right treatment options to combat the disease. The new technology will allow clinicians to monitor the disease progression using blood tests without the need for biopsies. The collaboration also comprises clinical oncology projects, one of them involving selumetinib. AstraZeneca will collaborate with the Babraham Institute, the Cancer Research UK Cambridge Institute and the University of Cambridge to identify and evaluate the best drug combinations for selumetinib in preclinical models of pancreatic cancer[1].

In June 2009, AstraZeneca and Merck entered a collaboration agreement to investigate the therapeutic potential of combining two investigational compounds, selumetinib and MK 2206 [*see RDI profile 800028810(MK 2206)*], as a new anticancer regimen. Under the terms of the agreement, AstraZeneca and Merck would collaborate to evaluate the co-administration of MK 2206 and selumetinib in a phase I trial in patients with solid tumours; all development costs will be shared. Opportunities for further clinical development would be assessed by the two companies on completion of the phase I trial[2].

In December 2003, Array and AstraZeneca announced a licensing and collaboration agreement to develop Array's MEK programme in the field of cancer. Under the terms of the agreement, Array will receive an upfront payment of $US10 million, research funding, potential development milestones of over $US85 million (dependent upon the number of successfully commercialised products) and royalties on product sales. AstraZeneca acquires exclusive rights to selumetinib and certain second-generation compounds for all oncology indications. Array is responsible for filing the IND, phase I clinical testing and certain aspects of process research for the development of selumetinib. In addition, Array is responsible for creating a select number of second-generation compounds, including cGMP manufacturing of phase I clinical materials. AstraZeneca will be responsible for all other aspects of clinical development and commercialisation[3].

AstraZeneca and the National Cancer Institute (USA) are collaborating on the clinical development of selumetinib for several cancer indications[4].

Key Development Milestones

Acute myeloid leukaemia An open-label, phase II trial in patients with recurrent or refractory acute myeloid leukaemia was initiated in the US (NCT00588809)[4]. Results were presented in December 2009. The status of this trial is unclear as the information has not been verified recently; however, the indication does not appear on the AstraZeneca company pipeline as of March 2015. Development is therefore assumed to have been discontinued[5][6][4].

Breast cancer Russian Academy of Medical Sciences plans a phase II trial to investigate the safety and efficacy of selumatinib when added to the docetaxel neoadjuvant chemotherapy in patients with early and locally advanced triple negative breast cancer (NCT02685657; ESR-14-10735). The trial will enrol participants in Russia[7].

Biliary cancer In November 2014, The University Health Network, Toronto, initiated a randomised phase II trial to assess the efficacy and safety of selumetinib, combined continuously or sequentially with cisplatin and gemcitabine, compared to cisplatin and gemcitabine alone, in patients with advanced biliary cancer (BIL-MEK; NCT02151084). The trial will enrol 15 patients in Canada[8].

A trial, sponsored by NCI, was initiated in patients with biliary cancer (NCT00553332). The status of this trial is unclear as the information has not been verified recently[9].

In May 2016, AstraZeneca discontinued a phase I trial, which was investigating the safety and tolerability of selumetinib in combination with cisplatin plus gemcitabine in Japanese patients with advanced biliary tract cancer (NCT01949870). The trial enrolled five patients and was discontinued due to change in the development strategy[10].

Colorectal cancer In March 2016, Antoni van Leeuwenhoek - Netherlands Cancer Institute, in collaboration with AstraZeneca and Pfizer, initiated the phase II SENSOR trial to evaluate the efficacy, safety and tolerability of each experimental agent, and to allocate patients with colorectal cancer and non-small cell lung cancer specific targeted agents using patient-derived tumour organoids (N14SNS; ABRNL50400.031.14; EudraCT2014-003811-13). The experimental agents are gefitinib, axitinib, AZD 5363, selumetinib, palbociclib, gedatolisib, glasdegib and vistusertib [*see Adis Insight Drug profiles* 800007340(Gefitinib), 800017408(Axitinib), 800018391(AZD 5363), 800030686(Glasdegib), 800020668(Palbociclib), 800030590(Gedatolisib) and 800031625(Vistusertib)]. The open-label trial is recruiting 70 patients in the Netherlands[11].

Selumetinib was investigated in a phase II clinical trial in previously-treated patients with K-ras or B-raf mutation-positive advanced or metastatic colorectal cancer (NCT01116271). The trial, which took place in the US, evaluated the drug in combination with irinotecan[12].

In August 2014, the National Cancer Institute initiated a phase I trial to investigate selumetinib in combination with cyclosporin A (CsA) in patients with advanced solid tumours with an expansion cohort in metastatic colorectal cancer (NCI-2014-01484; NCT02188264). Primary endpoint is dose limiting toxicities and maximum tolerated dose of the combination. The open-label trial was designed to enrol approximately 46 subjects in the US. As of January 2016, the study had completed enrolment and treatment of the combination of selumetinib and CsA in 18 patients. In April 2016, positive safety and efficacy data, including identification of a recommended phase II dose of selumetinib at 75 mg/kg two times a day and CsA at 2mg/kg was presented at the 107th Annual Meeting of the American Association for Cancer Research (AACR-2016)[13][14].

AstraZeneca has completed a phase II trial of selumetinib in patients with colorectal cancer in Brazil (NCT00514761). The study compared selumetinib with capecitabine in patients who have failed one or two prior chemotherapeutic regimens[15]. Results have been reported[16].

Glioma/Astrocytoma The National Cancer Institute has initiated a phase I/II dose-escalation study to assess the safety and stratum objective response of selumetinib in paediatric and adult subjects, up to 21 years of age (NCI-2012-03173; NCT0108910). The open-label trial is designed to enrol approximately 135 patients with glioma and astrocytoma in the US[17].

In June 2011, the National Cancer Institute initiated a phase I/II trial of selumetinib in paediatric and adult subjects up to 21 years of age (11-C-0191; 110191; NCT01386450). The primary endpoints to be assessed are safety and maximum tolerated dose. Secondary endpoints include pharmacokinetics and biomarker analysis. The non-randomised, open-label trial is designed to enrol 18 patients with glioma and astrocytoma in the US[17].

Hepatocellular carcinoma In April 2015, the phase II portion of a Singapore-based phase I/II trial of selumetinib in patients with inoperable hepatocellular carcinoma was terminated, due to financial reasons (09-20-HEP; NCT01029418). Enrolment of 166 patients in phase I portion of the trial was completed in November 2012. The trial was being conducted as part of a clinical development collaboration with two of Singapore's leading research institutions, the National Cancer Centre Singapore (NCCS) and the National University Hospital (NUH). A memorandum of understanding (MOU) has been signed in connection with this agreement which AstraZeneca hopes will speed up development in Asia[18][19].

A phase II trial of selumetinib in patients with advanced or metastatic hepatocellular carcinoma in the US was terminated by the National Cancer Institute in 2011 after an interim analysis showed no radiographic response (NCT00604721)[20].

Malignant melanoma Development of selumetinib as a monotherapy and combination therapy for malignant melanoma appears to have been discontinued; these indications are not listed on the AstraZeneca company pipeline as of March 2015.

AstraZeneca completed a randomised, double-blind phase II trial in June 2013, which compared combination therapy comprising selumetinib and dacarbazine with dacarbazine alone for the first-line treatment of patients with malignant melanoma (NCT00936221). The trial enrolled 385 patients with BRAF positive advanced cutaneous or unknown primary melanoma at sites in the US, Brazil, Czech Republic, France, Germany, Hungary, Netherlands, Norway, Spain, Sweden, Switzerland and the UK[21][22][23][24][25].

Initial results from a phase II trial in patients with malignant stage III/IV melanoma showed that selumetinib did not improve progression free survival compared with temozolomide (NCT00338130). Based on these results, AstraZeneca does not plan to progress selumetinib as a monotherapy into phase III trials for this indication[26][27][28][29]. However, a study conducted by Memorial Sloan Kettering Center showed progression-free survival of nearly 16 weeks in patients who received selumetinib, with 50% achieving tumour shrinkage[30].

A phase I study of selumetinib in patients with melanoma and other solid tumours has been completed[29][31][32].

Multiple myeloma Development of selumetinib in this indication was not listed on the AstraZeneca company pipeline, as of March 2015, and appears to have been discontinued.

A phase II trial of selumetinib in patients with multiple myeloma has been completed in the US (NCT01085214)[4][33].

Non-small cell lung cancer (NSCLC) AstraZeneca has terminated the development of selumetinib as a second-line therapy for KRAS mutation-positive NSCLC, due to negative results from safety and efficacy studies (AstraZeneca pipeline, November 2016). AstraZeneca had intended to file for regulatory approval in this indication in the US and EU in the first half of 2017. The filings were to be supported by the results of the SELECT-1 trial; however, the trial did not meet its primary endpoint [*see below*] (AstraZeneca pipeline, April 2016)[34][35].

A phase III trial of selumetinib as a first-line treatment in KRAS mutation-positive NSCLC is being considered by AstraZeneca[36]. Array BioPharma reported in November 2014, that AstraZeneca is conducting two clinical trials of sunitinib, in combination with MEDI 4736, an anti-PD-L1 antibody, and AZD 9291, a mutant-selective EGFR inhibitor[37][38].

In August 2016, AstraZeneca reported that a pivotal phase III trial of selumetinib for the treatment of patients with locally advanced or metastatic KRAS-mutant NSCLC, did not meet its primary endpoint of progression-free survival (PFS). No significant effect on overall survival (OS) was observed and the adverse event profiles for selumetinib and docetaxel were consistent (SELECT-1; NCT01933932; EudraCT2013-001676-38)[34][39]. The phase III trial was initiated in September 2013 which investigated the safety and efficacy of selumetinib in combination with docetaxel as second-line treatment, in patients with NSCLC. This randomised, open-label, double-blind enrolled 3323 patients in the EU, the US, Canada, South America, Australia, Brazil, Russia, Turkey, Ukraine and Israel and completed enrolment in January 2016. Results from the trial were presented at the 41st European Society for Medical Oncology Congress (ESMO-2016)[40][1][30][21][41]. The first patient randomised in the trial was announced in October 2013[42][43]. The initiation of this trial triggered a $US5 million payment from AstraZeneca to Array[44][45].

University of Texas M.D. Anderson Cancer Center in collaboration with MedImmune and AstraZeneca plans to initiate a phase II trial to evaluate safety and efficacy of durvalumab in combination with selumetinib in patients with KRAS mutant NSCLC (2016-0060; NCT03004105). The randomised, parallel, open-labelled trial is designed to enrol approximately 76 patients in the US[46].

OHSU Knight Cancer Institute, in collaboration with the National Cancer Institute, plans a phase I trial to evaluate the safety of selumetinib, in combination with albumin-bound paclitaxel [*see RDI*

Profile 800016962(Albuminbound paclitaxel)], as a second line therapy in patients with stage IIIB-IV non-small cell lung cancer (IRB00011462; NCI-2015-01018; NCT02503358). The randomised, open-label trial is designed to enrol approximately 54 patients in the US[47].

In June 2016, AstraZeneca completed a randomised, open-label phase IIa trial, which investigated the efficacy of gefitinib, osimertinib, selumetinib plus docetaxel, and tremelimumab, with switch to durvalumab, in patients with locally advanced or metastatic NSCLC (D4191C00011; NCT02179671) [*see RDI Profiles 800007340(Gefitinib), 800037784(Osimertinib), 800020650(Tremelimumab), 800037095(Durvalumab)*]. The trial was initiated in July 2014 and enrolment of 40 patients was completed in the US in October 2015[48].

Top-line results from 87 patients who completed a phase II trial showed that a numerically greater increase overall survival (primary endpoint) was observed among recipients of selumetinib plus docetaxel, compared with docetaxel alone; though the between group difference was not significant. In addition, significant improvements in key secondary endpoints (progression-free survival, objective response rate, and alive and progression-free at 6 months) favoured treatment with selumetinib plus docetaxel[49][22][50]. The trial was conducted in patients with KRAS mutation-positive NSCLC in the US, Belgium, Brazil, Bulgaria, Canada, the Czech Republic, Denmark, France, Hungary, Italy, Mexico, Peru and Spain (NCT00890825; EudraCT2008-006323-31; Study 16)[26][23][24].

AstraZeneca initiated a randomised, double-blind, placebo-controlled phase II trial in December 2012 to investigate second-line selumetinib in combination with docetaxel, versus docetaxel alone, in patients with locally advanced or metastatic (stage IIIb to IV) NSCLC (NCT01750281; EudraCT2012-003622-25). Enrolment of 265 patients was initiated in Hungary and Germany, but enrolment was suspended in August 2013, in order for a new study design to be implemented. Recruitment resumed in February 2014 in the US, France, Germany and Hungary[51].

The National Cancer Institute (an official collaborator) is conducting a phase II trial to evaluate the efficacy of selumetinib monotherapy and selumetinib + erlotinib in patients with KRAS wild type and KRAS-mutant advanced NSCLC (NCT01229150). Approximately 100 patients will be recruited in the US[52].

A phase II trial of selumetinib in patients with NSCLC, which compared selumetinib with pemetrexed in the second- or third-line treatment of advanced NSCLC, showed that there was a significant difference between groups for the primary disease progression endpoint (NCT00372788) [53][54].

In January 2015, AstraZeneca initiated an open-label phase II study to evaluate selumetinib in combination with cisplatin and pemetrexed compared with cisplatin plus pemetrexed chemotherapy in patients with advanced or metastatic KRAS wild-type or unknown NSCLC (I219; NCT02337530). Selumetinib plus cisplatin plus pemetrexed will be administered as continuous and intermittent schedule. The randomised trial will enrol approximately 140 patients in Canada[55].

In August 2014, AstraZeneca initiated the phase Ib TATTON trial designed to evaluate the safety, efficacy, pharmacokinetics and tolerability of mereletinib in combination with continuous and with intermittent ascending doses of selumetinib in patients with EGFR mutation positive late-stage NSCLC who have progressed following therapy with an EGFR TKI (D5160C00006; NCT02143466). The open-label, parallel-group trial will enrol 240 patients in the US, Japan, South Korea and Taiwan[56]. In May 2015, AstraZeneca presented tolerability and safety results from the study at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO-2015)[57].

AstraZeneca completed a dose escalation phase I trial in January 2016 (SELECT-3; NCT01809210; EudraCT2012-005202-22). This UK-based trial was initiated in April 2013, and assessed the tolerability and preliminary efficacy of oral selumetinib given twice daily when combined with standard intravenous first-line platinum-containing doublet chemotherapy in 76 patients with advanced NSCLC. Preliminary data from this trial were reported at the 39th Congress of the European Society for Medical Oncology (ESMO-2014). Additional results in 55 evaluable patients from the trial were presented at the 41st European Society for Medical Oncology Congress, which demonstrated a similar pharmacokinetic profile for selumetinib across the combination regimens[58][37][59].

In collaboration with AstraZeneca, the NCIC Clinical Trials Group initiated an open-label phase Ib trial in January 2013 to investigate the safety, pharmacokinetics and preliminary efficacy of selumetinib in previously treated or untreated patients with advanced or metastatic NSCLC (NCT01783197). Selumetinib is being given in combination with either pemetrexed, paclitaxel and carboplatin, or pemetrexed and cisplatin. The trial will enrol 68 patients in Canada[60].

In May 2015, AstraZeneca completed an open-label phase I trial of selumetinib in combination with docetaxel as a second-line therapy for locally advanced or metastatic NSCLC (stage IIB-IV) in Japanese patients (NCT01605916). The open-label trial was initiated in June 2012 and enrolled 33 patients in Japan[61].

Neurofibromatoses Array BioPharma reported that a pivotal phase II trial initiated by the National Cancer Institute in December 2015 was progressing as of August 2016 (NCI-2015-00456; 160043; 16-C-0043; NCT02644512; NCT02407405). The open-label trial designed to evaluate the efficacy of selumetinib in adult patients with neurofibromatoses type 1 and inoperable plexiform neurofibromas will enrol 50 patients in the US[62][63].

In May 2011, a phase I/II dose-escalation trial of selumetinib in paediatric subjects, with neurofibromatosis, was initiated in the US (110161; 11-C-0161; NCT01362803). The open-label, non-randomised study is sponsored by the National Cancer Institute and is designed to enrol 30 patients. In June 2014, preliminary results from the trial were presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO-2014)[64][38][65]. Results of the phase II part from a phase I/II trial in paediatric patients with neurofibromatoses are expected in 2015, as reported by Array BioPharma[66].

The National Cancer Institute plans to initiate a pilot clinical trial to assess the efficacy of selumetinib in adult patients with neurofibromatoses type 1 and dermal neurofibromas (NCI-2016-01087; 9990; P30CA013148; NCT02839720). The open-label, single-group trial will enrol approximately 24 patients in the US[67].

Pancreatic cancer AstraZeneca is collaborating with the Babraham Institute, the Cancer Research UK Cambridge Institute and the University of Cambridge to identify and evaluate the best drug combinations for selumetinib in preclinical models of pancreatic cancer[1]. According to the AstraZeneca 2014 annual report, this collaboration is ongoing.

AstraZeneca completed a phase II trial of selumetinib monotherapy in patients with advanced or metastatic pancreatic cancer who had failed first-line therapy with gemcitabine (NCT00372944). This trial took place at centres in the US, Australia, Bulgaria, Hungary and Romania[68]. Development of selumetinib as monotherapy for the treatment of pancreatic cancer appears to have been discontinued; this indications was not listed on the AstraZeneca company pipeline as of March 2015.

The National Cancer Institute plans to initiate a phase II trial to evaluate the safety and efficacy of selumetinib 100mg bid in patients with advanced pancreas cancer with KRAS G12R mutations (NCI-2017-00118; 10050; ZIABC011078; NCT03040986). The open-label, single-group trial will enrol approximately 180 patients in the US[69].

Thyroid cancer According to AstraZeneca's April 2016 pipeline, regulatory filings for selumetinib for the treatment of differentiated thyroid cancer are planned in the US and the EU in 2018. The filings will be supported by the results of the ASTRA trial.

In August 2013, AstraZeneca initiated the pivotal phase III ASTRA trial to investigate the efficacy of oral selumetinib in combination with radioactive iodine in patients with differentiated thyroid cancer (NCT01843062; EudraCT 2013-000423-14). Recruitment of approximately 304 patients for this randomised, double blind study is ongoing in the US, Denmark, France, Brazil, Germany, Italy, Poland and Sweden. The trial was initiated as phase II trial, but in April 2014, the company upgraded it to phase III. The phase III trial was ongoing as of August 2016[62][21][30][70].

A phase II trial, sponsored by the National Cancer Institute (NCI), is investigating the efficacy and tolerability of selumetinib monotherapy in patients with iodine-131 refractory papillary thyroid cancer or papillary thyroid cancer with follicular elements (NCT00559949). The primary endpoint is objective response rate (complete response and partial response). Enrolment of 22 patients appears to have been completed in the US and Canada. The trial was verified in May 2015 to be ongoing[71].

Academic and Community Cancer Research United, in collaboration with National Cancer Institute, has planned to initiate a phase II trial to study how well iodine I-131 works with or without selumetinib in treating patients with thyroid cancer that has returned or has spread from where it started to other places in the body (NCT02393690). The randomised, double-blind trial was designed to enrol approximately 90 patients in the US[72].

In February 2015, Sheffield Teaching Hospitals NHS Trust and AstraZeneca initiated the phase II SEL-I-METRY trial which was supposed to evaluate whether treatment with selumetinib increased uptake of radioactive iodine in patients with previously iodine refractory thyroid cancer (15EM0455; STH18441; ISRCTN17468602; UKCRN19937; EudraCT2015-002269-47). The single-armed trial intends to enrol approximately 60 patients in the UK[73].

Genzyme and AstraZeneca collaborated with researchers from Memorial Sloan-Kettering Cancer Center in a pilot study to examine if selumetinib can improve uptake of radioactive iodine in patients with metastatic thyroid cancer (NCT00970359). The trial began in September 2009, enrolled 22 patients and was completed in April 2013[74].

In May 2016, the US FDA granted orphan drug designation to selumetinib for the treatment of differentiated thyroid cancer[75].

Uveal melanoma Regulatory submissions for selumetinib in this indication were planned in the US and the EU in late 2015, based on the results of the pivotal SUMIT trial[36]. However, AstraZeneca reported in its pipeline of June 2015 that it had discontinued development in this indication, as the SUMIT trial had failed to meet its primary endpoint.

In October 2016, AstraZeneca completed the phase III SUMIT trial in patients with metastatic uveal melanoma (NCT01974752; EudraCT2013-003545-41; D1344C00001). In July 2015, AstraZeneca reported that the phase III SUMIT trial did not meet its primary endpoint of progression free survival in patients with metastatic uveal melanoma[76]. In May 2015, AstraZeneca completed enrolment in the trial that assessed the efficacy, safety and tolerability of selumetinib in combination with dacarbazine, in patients with metastatic uveal melanoma. The randomised, double-blind, placebo-controlled trial enrolled 152 patients in the US, the UK, Belgium, Canada, Czech Republic, Finland, France, Germany, Israel, The Netherlands and Spain. The trial was initiated in February 2014 as phase II trial, but in April 2014, the company upgraded the trial to phase III[66][77][78][44][79].

In April 2015, the University of Liverpool and AstraZeneca initiated a phase II study to investigate continuous selumetinib, compared with continuous or interrupted selumetinib in combination with weekly paclitaxel, in patients with metastatic uveal melanoma (EudraCT2014-004437-22; SelPac Version 1). The study intended to enrol approximately 123 subjects in the United Kingdom[80].

In April 2015, selumetinib was granted orphan drug designation by the US FDA for the treatment of uveal melanoma[81].

Solid tumours (combination therapy) The Netherlands Cancer Institute has initiated a phase I/II trial to assess selumetinib and afatinib in patients with late-stage colorectal, pancreatic and non-small cell lung cancer, who have failed first-line therapy (EudraCT2014-001855-22; M14AFS). The randomised, open-label trial is expected to enrol approximately 320 patients in Netherlands

In December 2015, AstraZeneca initiated a phase I trial to investigate the safety, tolerability, pharmacokinetics and anti-tumour activity of ascending doses of selumetinib in combination with durvalumab [*see RDI profile*
800037095(Durvalumab)] in patients with advanced solid tumour (NCT02586987; D1345C00003). The open-label, non-randomised trial will be enrolling approximately 40 patients in the US[82].

A phase I trial of selumetinib in combination with standard doses of selected chemotherapies has been initiated by AstraZeneca in patients with advanced solid tumours in the US (NCT00600496). The open-label, non-randomised trial enrolled 140 patients. There are four study arms and selumetinib is being administered orally, twice daily, in combination with docetaxel, dacarbazine, erlotinib or temsirolimus[83]. Study results for the selumetinib plus docetaxel arm were reported by AstraZeneca at the 23rd AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2011)[84].

AstraZeneca and Merck & Co initiated a phase I trial in November 2009, to investigate the safety of selumetinib and MK 2206 [*see RDI profile 800028810(MK 2206)*], in patients with locally advanced or metastatic solid tumours (NCT01021748). However, the trial was terminated in late 2012, and reinitiated in August 2013, and was completed in July 2014. The trial had enrolled 63 patients in the US and the UK[85][86].

Trials in other indications/in healthy volunteers In April 2015, AstraZeneca completed a phase I study to evaluate the bioavailability of variants of selumetinib capsule compared with that of a reference selumetinib capsule, in healthy volunteers (D1532C00078; NCT02322749). The randomised, open-label trial was initiated in February 2015 and enrolled 48 healthy male volunteers in the UK[87].

At the AACR-2012 meeting in April 2012, the Gynecologic Oncology Group reported results from a phase II trial assessing selumetinib in 52 women with low-grade serous ovarian or peritoneal cancer (NCT00551070). The trial was funded by the National Cancer Institute[88][89].

In October 2014, AstraZeneca completed a phase I trial that evaluated the absolute bioavailability of oral selumetinib in healthy male volunteers (D1532C00080; NCT02238782). The open-label trial enrolled 21 volunteers in the UK[90].

AstraZeneca initiated a phase I trial in February 2014 to study the effect of rifampicin on the pharmacokinetics of selumetinib in healthy male volunteers (D1532C00085; NCT02046850). The trial enrolled 24 subjects in the US and was completed in April 2014[91].

In October 2013, AstraZeneca initiated an open-label, phase I trial to evaluate the absorption, distribution, metabolism and excretion (ADME) of a single dose of an orally administered, radioactive [14C] formulation of selumetinib (NCT01931761). The trial enrolled six healthy volunteers in the UK and was completed in November 2013[92].

AstraZeneca completed a phase I trial in May 2014, which investigated the pharmacokinetics, safety and tolerability of oral selumetinib 25, 50 and 75mg in approximately 117 Japanese and non-Japanese Asian healthy males in the UK (NCT01960374)[93].

In July 2012, AstraZeneca initiated a phase I trial in the US in healthy volunteers to compare the pharmacokinetics of three different formulations of selumetinib (two capsule formulations and an oral solution formulation) (NCT01635023). The trial recruited 27 participants and was completed in October 2012[94].

In April 2014, AstraZeneca initiated an open-label phase I trial to evaluate the effect of itraconazole and fluconazole on the pharmacokinetics of selumetinib in healthy male volunteers (D1532C00083; NCT02093728). The trial enrolled 26 subjects in the US and was completed in June 2014[95].

AstraZeneca completed an open-label phase I study in July 2014 that assessed the safety, tolerability and pharmacokinetics of selumetinib in patients with renal impairment and healthy volunteers (NCT02063204; D1532C00081). Approximately 48 participants were recruited in the US[96].

In November 2014, AstraZeneca completed an open-label phase I trial, which evaluated the pharmacokinetics, safety and tolerability of selumetinib in healthy volunteers and patients with mild, moderate and severe hepatic impairment (NCT02063230; D1532C00082). The trial was initiated in March 2014 and enrolled 34 participants in the US[97].

In March 2014, AstraZeneca initiated a randomised, double-blind, crossover phase I trial to assess the effect of single oral doses of selumetinib on the QTc interval in healthy volunteers (NCT02056392). The trial included an active comparator (moxifloxacin) and a placebo comparator. The trial enrolled approximately 54 subjects in the US and was completed in August 2014[98].

AstraZeneca completed a phase I trial in February 2014, which investigated the effect of food on the pharmacokinetics of selumetinib in approximately 34 healthy volunteers in the US (NCT01974349)[99].

Drug Properties & Chemical Synopsis

Route of administration PO

Formulation Capsule

Class Antineoplastics, Benzimidazoles, Small molecules

Mechanism of Action MAP kinase kinase 1 inhibitors; MAP kinase kinase 2 inhibitors

WHO ATC code

L01X-E (Protein kinase inhibitors)

EPhMRA code

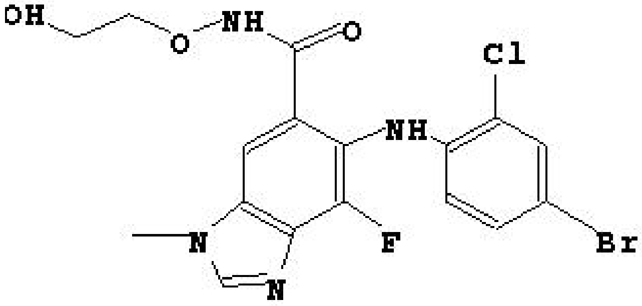
L1H (Protein Kinase Inhibitor Antineoplastics)

Chemical name 5-[(4-Bromo-2-chlorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide

Molecular formula C17 H15 Br Cl F N4 O3

SMILES C12C=C(C(=C(C=1N=CN2C)F)NC1C=CC(=CC=1Cl)Br)C(NOCCO)=O

Chemical Structure



CAS Registry Number 606143-52-6

Biomarker

Drug Name	**Biomarker Name**	**Biomarker Function**
Selumetinib	***A1C***	not specified
	AKT	Outcome Measure
	Angiopoietin 2	Outcome Measure
	Bcl-2	Outcome Measure
	BNP	Outcome Measure, Safety
	BRAF	Exclusion, Inclusion, Outcome Measure
	C-Kit	Outcome Measure
	c-Met	not specified
	CA-125	Outcome Measure
	CA-19-9	Inclusion, Outcome Measure
	Caspase 3	Outcome Measure
	CD4	Outcome Measure
	codanin 1	Outcome Measure, Safety
	CRAF	not specified
	EGFR	Exclusion, Inclusion, Outcome Measure, Safety
	ER alpha	not specified
	FBJ murine osteosarcoma viral oncogene homolog	Outcome Measure
	FGFR1	not specified
	FGFR2	not specified
	FGFR3	not specified
	FGFR4	not specified
	Flt-3	Inclusion, Outcome Measure
	GNA11	Inclusion, Outcome Measure
	HER2	Exclusion, Outcome Measure
	HRAS	not specified
	IL1 beta	Outcome Measure
	IL6	Outcome Measure
	Ki67	Outcome Measure
	KRAS	Inclusion, Outcome Measure, Safety
	LKB1	not specified
	MAPK1	Outcome Measure
	MEK1	not specified
	MEK2	not specified
	midline 1	Outcome Measure
	mTOR	not specified
	neuregulin 1	not specified
	neurofibromin 1	not specified
	NRAS	Outcome Measure
	PGR	Outcome Measure
	PIK3CA	not specified
	PTEN	not specified

RET	not specified
RPS6	Outcome Measure
TNF-alpha	Outcome Measure
troponin I, cardiac	Outcome Measure, Safety
WW domain containing oxidoreductase	Inclusion, Outcome Measure

For more detail, check out ***BiomarkerBase:*** the leading source of information about biomarkers used in drug development and diagnostic tests, tracking over 314005 biomarker uses worldwide by over 860 companies

Trial Landscape

Indication	Phase 0	Phase I	Phase II	Phase III	Phase IV
Pancreatic cancer	-	11	6	-	-
Skin cancer	-	12	7	-	-
Gallbladder cancer	-	1	2	-	-
Advanced breast cancer	-	-	2	-	-
Thyroid cancer	-	9	5	1	-
Cholangiocarcinoma	-	-	1	-	-
Leiomyosarcoma	-	-	1	-	-
Glioma	-	3	1	-	-
HIV infections	-	-	1	-	-
Soft tissue sarcoma	-	-	2	-	-
Diffuse large B cell lymphoma	-	-	1	-	-
Kaposi's sarcoma	-	-	1	-	-
Acute myeloid leukaemia	-	9	1	-	-
Adenocarcinoma	-	-	4	-	-
Renal cancer	-	-	1	-	-
Rectal cancer	-	2	-	-	-
Squamous cell cancer	-	-	1	-	-
Cancer	-	34	52	4	-
Colon cancer	-	-	1	-	-
Ovarian cancer	-	-	2	-	-
Peritoneal cancer	-	-	1	-	-
Colorectal cancer	-	16	7	-	-
Connective and soft tissue neoplasms	-	1	2	-	-
Gastric cancer	-	1	1	-	-
Oesophageal cancer	-	1	1	-	-
Plexiform neurofibroma	-	-	1	-	-
Non-small cell lung cancer	-	15	13	2	-
Lung cancer	-	16	13	2	-
Solid tumours	-	23	2	-	-
Malignant melanoma	-	12	6	-	-
Liver cancer	-	8	3	-	-
Biliary cancer	-	10	3	-	-
Astrocytoma	-	3	1	-	-
Breast cancer	-	-	5	-	-

Endometrial cancer	-	-	2	-	-
Uveal melanoma	-	4	3	1	-
Neurofibromatoses	-	1	3	-	-
Multiple myeloma	-	8	1	-	-
Neurofibroma	-	1	3	-	-

Development Status

Summary Table

Indication	Patient Segment	Phase	Countries	Route / Formulation	Developers	Event Date
Acute myeloid leukaemia	Recurrent	Discontinued (II)	USA	PO / Capsule	National Cancer Institute (USA)	31 Mar 2015
Astrocytoma	In adolescents, In adults, In children	Phase I/II	USA	PO / Capsule	National Cancer Institute (USA)	01 Jun 2011
Biliary cancer	Combination therapy, Late-stage disease, Metastatic disease	Phase II	Canada	PO / Capsule	University Health Network	01 Nov 2014
Biliary cancer	Combination therapy, Inoperable/Unresectable, Metastatic disease	Phase I	Japan	PO / Capsule	AstraZeneca	01 Oct 2013
Biliary cancer	Inoperable/Unresectable	No development reported (II)	USA	PO / Capsule	National Cancer Institute (USA)	22 Jun 2015
Colorectal cancer	Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase II	Netherlands	PO / Capsule	Netherlands Cancer Institute	23 Mar 2016
Colorectal cancer	Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase II	USA	PO / Capsule	AstraZeneca	30 Apr 2010
Colorectal cancer	Metastatic disease, Second-line therapy or greater	No development reported (II)	Brazil	PO / Capsule	AstraZeneca	22 Jun 2015
Glioma	In adolescents, In adults, In children	Phase I/II	USA	PO / Capsule	National Cancer Institute (USA)	01 Apr 2010
Hepatocellular carcinoma	Combination therapy, First-line therapy, Late-stage disease	Discontinued (II)	Singapore	PO / Capsule	National Cancer Centre (Singapore)	01 Apr 2015
Hepatocellular carcinoma	First-line therapy, Late-stage disease, Monotherapy	Discontinued (II)	USA	PO / Capsule	National Cancer Institute (USA)	31 Oct 2007
Malignant melanoma	First-line therapy, Late-stage disease, Monotherapy	Discontinued (II)	World	PO / Capsule	AstraZeneca	20 Dec 2007

Malignant melanoma	Combination therapy, First-line therapy	Discontinued (II)	Brazil, Czech Republic, France, Germany, Hungary, Netherlands, Norway, Spain, Sweden, Switzerland, USA, United Kingdom	PO / Capsule	AstraZeneca	22 Jun 2015
Multiple myeloma	-	Discontinued (II)	USA	PO / Capsule	National Cancer Institute (USA)	31 Mar 2015
Neurofibromatoses	In adults, Inoperable/Unresectable	Phase II	USA	PO / Capsule	National Cancer Institute (USA)	01 May 2015
Neurofibromatoses	In adolescents, In children	Phase I/II	USA	PO / Capsule	National Cancer Institute (USA)	01 May 2011
Non-small cell lung cancer	Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase II	Netherlands	PO / Capsule	Netherlands Cancer Institute	23 Mar 2016
Non-small cell lung cancer	Combination therapy, Late-stage disease	Phase II	USA	PO / Capsule	AstraZeneca	31 Jul 2014
Non-small cell lung cancer	Combination therapy, First-line therapy, Late-stage disease	Phase I	United Kingdom	PO / Capsule	AstraZeneca	09 Apr 2013
Non-small cell lung cancer	Combination therapy, First-line therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase I	Canada	PO / Capsule	AstraZeneca	31 Jan 2013
Non-small cell lung cancer	Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase I	Japan	PO / Capsule	AstraZeneca	14 Jun 2012
Non-small cell lung cancer	Combination therapy, Late-stage disease, Second-line therapy or greater	Phase I	South Korea, Taiwan	PO / Capsule	AstraZeneca	01 Aug 2014

Non-small cell lung cancer	Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	No development reported (II)	Czech Republic, Denmark	PO / Capsule	AstraZeneca	22 Jun 2015
Non-small cell lung cancer	Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	Discontinued (III)	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, USA, Ukraine, United Kingdom	PO / Capsule	AstraZeneca	17 Nov 2016
Pancreatic cancer	Combination therapy	Preclinical	United Kingdom	PO / Capsule	University of Cambridge	09 Jul 2012
Pancreatic cancer	Late-stage disease, Metastatic disease, Monotherapy, Second-line therapy or greater	Discontinued (II)	Australia, Bulgaria, Hungary, Romania, USA	PO / Capsule	AstraZeneca	22 Jun 2015
Solid tumours	Combination therapy, Late-stage disease, Second-line therapy or greater	Phase I	United Kingdom	PO / Capsule	Merck & Co	01 Nov 2009
Solid tumours	Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater	Phase I	USA	PO / Capsule	Merck & Co	18 Jun 2004
Thyroid cancer	Combination therapy	Phase III	Brazil, Denmark, France, Germany, Italy, Poland, Sweden, USA	PO / Capsule	AstraZeneca	04 Nov 2014
Thyroid cancer	Monotherapy	Phase II	Canada, USA	PO / Capsule	National Cancer Institute (USA)	31 Jan 2007

Uveal melanoma	Combination therapy, First-line therapy, Metastatic disease	Discontinued (III)	Belgium, Canada, Czech Republic, Finland, France, Germany, Israel, Netherlands, Spain, USA, United Kingdom	PO / Capsule	AstraZeneca	30 Jun 2015
Uveal melanoma	Combination therapy, Monotherapy, Second-line therapy or greater	Discontinued (II)	United Kingdom	PO / Capsule	University of Liverpool	30 Jun 2015

Orphan Status

Indication	Patient Segment	Country	Organisation	Event Date
Thyroid cancer	-	USA	AstraZeneca	12 May 2016
Uveal melanoma	-	USA	AstraZeneca	17 Apr 2015

Commercial Information

Involved Organisations

Organisation	Involvement	Countries
Array BioPharma	Originator	USA
Array BioPharma	Owner	USA
AstraZeneca	Licensee	World
University Health Network	Collaborator	Canada
National Cancer Centre (Singapore)	Collaborator	Singapore
National Cancer Institute (USA)	Collaborator	USA
Sheffield Teaching Hospitals NHS Foundation Trust	Collaborator	United-Kingdom
National University Hospital (Singapore)	Collaborator	Singapore
University of Liverpool	Collaborator	United-Kingdom
Netherlands Cancer Institute	Collaborator	Netherlands
Cancer Research UK	Collaborator	United-Kingdom
University of Cambridge	Collaborator	United-Kingdom

Credit Suisse Market Status

Indication	Region	Company	Phase	Expected Launch Year	Probability of Success%	Patent Expiry Year	Expected Generic Entry	Last Update
Cancer - Lung	Wrld (50% US)	AstraZeneca	Development Stopped	-	-	-	-	14 Sep 2016
Cancer - Thyroid	Wrld (50% US)	AstraZeneca	III	2019	25	-	-	14 Sep 2016
Cancer-melanoma/liver	US	AstraZeneca, Merck	III	2016	30	-	-	10 Oct 2013
Cancer-Uveal melanoma	Wrld (50% US)	AstraZeneca	Development Stopped	-	-	-	-	14 Sep 2016

Credit Suisse Financial Forecast

Indication	Region	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Last Update
Cancer - Thyroid	Wrld (50% US)	0	0	0	0	0	0	0	0	25	50	14 Sep 2016
Cancer-melanoma/liver	US	0	0	0	0	0	50	100	125	144	158	10 Oct 2013
Total		0	0	0	0	0	50	100	125	169	208	

* All values in US$ millions

Related Safety Reports

Adverse drug reaction	Total safety reports	Serious reports	First reports
Cardiovascular disorders	1	-	-
Chemically induced disorders	3	2	1
Digestive system disorders	2	1	1
Eye disorders	2	2	-

Immunological disorders	***3***	***2***	***1***
Infections	***3***	***1***	***1***
Musculoskeletal disorders	***1***	***1***	-
Neurological disorders	***2***	***1***	-
Pathological conditions signs and symptoms	***4***	***2***	***1***
Pigmentation	***1***	-	-
Signs symptoms and ill defined conditions	***2***	***1***	-
Skin and connective tissue diseases	***6***	***2***	***1***
Stomatognathic disorders	***1***	-	-
Tissue disorders	***1***	***1***	-

Scientific Summary

Adverse Events Frequent: Diarrhoea; Skin eruptions
Occasional: Anoxia; Blurred vision; Fatigue; Nausea; Oedema; Taste disorders; Vomiting
Rare: Dehydration

Pharmacokinetic Measures

Characterstic	Measure
$T_{½beta}$ (h)	7.62 - 13.5
T_{max} (h)	1.16 - 2.63

Pharmacokinetics

A phase I trial in patients with advanced cancer demonstrated that the AUC and C_{max} of the Hyd-sulfate solid oral formulation of selumetinib 75 mg was at least as high as those for the free base oral suspension of selumetinib 100 mg. The preliminary geometric mean C_{max} and $AUC_{0-\infty}$ of the selumetinib 75 mg Hyd-sulfate solid oral formulation and the selumetinib 100 mg free base oral suspension were 1307 (76.3) ng/mL and 4742 (34.1) ng.h/mL, and 523 (91.1) ng/mL and 2559 (66.6) ng.h/mL, respectively[105].

In a phase Ib trial in 34 patients with solid tumours, trough plasma concentrations of selumetinib was 400 ng/ml[32].

The single dose pharmacokinetics of oral selumetinib (50-300mg bid for 28-day cycles) showed dose-related plasma concentration and AUC_{0-12h} values. The maximal concentration of 0.59-1.26 µg/mL was reached at 1.16-2.63h. The $t_{½}$ values were in the range of 7.62-13.5h[107].

Adverse Events

Biliary cancer

Phase II interim data from a phase II study of selumetinib in patients with advanced biliary cancer have shown that the drug had acceptable tolerability. The study was conducted at four institutions in the US. Patients received oral selumetinib (100mg bid) on a daily basis. A total of 29 patients completed accrual into the study; 28 patients were evaluable for the toxicity and survival. Thirty-nine percent of patients had received one prior therapy. Toxicities were mild (mostly grade 1 or 2) with rash (skin eruptions; 65%) and diarrhoea (53%) being the most frequent events[102].

Colorectal cancer

Phase II in an exploratory trial comparing selumetinib (100mg bid) with capecitabine (1250 mg/m^2 bid) in 69 patients, 97% experienced AEs. The most common AEs with selumetinib were dermatitis acneform (56%), diarrhea (44%), asthenia (29%) and peripheral edema (26%). Eleven serious AEs were experienced in each group[16].

Phase I The combination of selumetinib and cyclosporin A (CsA) was well tolerated in the phase Ib study of the combination of selumetinib and cyclosporin A. In cohort 1 one dose limiting toxicity (DLT) of grade three hypertension, and in cohort 2 three DLTs of grade three hypertension, rash and elevated creatinine were reported (n = 12). Grade 1 or 2 nausea (67 %) and rash (50 %) were observed as the most common adverse events. The data was reported from 18 metastatic colorectal cancer patients treated with the combination selumetinib and cyclosporin A[13][14].

Glioma/Astrocytoma Administration of selumetinib was found to be safe, well tolerated and showed reversible toxicities in patients with neurofibromatosis during a phase I trial. Commonly reported adverse events were acneiform rash, nausea, vomiting, asymptomatic CPK elevation, diarrhoea, abdominal pain and fatigue[64][38].

Non-small cell lung cancer (NSCLC)

Phase III Results from the phase III SELECT-1 trial demonstrated that 346 patients (68%) died with adverse events reported by 99% and 95% patients in the selumetinib + docetaxel and placebo + docetaxel, respectively. Grade 3 AE were more frequent in the selumetinib + docetaxel group (67%) as compared to placebo + docetaxel group (45%). Serious AE (SAE) and AE leading to hospitalisation were more frequent in the selumetinib + docetaxel group (49% and 46%) than placebo + docetaxel group (32% and 30%)[40].

Grade 3 or 4 neutropenia and febrile neutropenia and Grade 1 or 2 diarrhoea was more prevalent in patients who received selumetinib in combination with docetaxel, compared with docetaxel alone in a randomised phase II trial in 87 patients with KRAS-mutant NSCLC[49].

Phase I According to results from a phase I trial, fatigue, nausea, diarrhoea and vomiting were observed in 55 evaluable patients. 30 (55%) patients showed grade III or higher selumetinib-related AEs. Dose-limiting toxicities were observed in one patient each, for cohort 2 patients who showed grade IV thrombocytopenia/epistaxis and grade IV thrombocytopenia; in cohort 3 patients, who showed grade IV anaemia; in cohort 6 patients who displayed grade III lethargy; and in cohort 7 patients, who showed grade IV febrile neutropenia. There were nine deaths, which were causally unrelated to selumetinib. Earlier, treatment with selumetinib, in combination with standard intravenous first-line platinum-containing doublet chemotherapy, was well tolerated in patients with advanced NSCLC, in the trial. Adverse event profile was consistent with the known side-effects associated with each of the components of treatment. These preliminary data were from 20 patients, who were available for evaluation at the time of reporting these data. These patients were not treated with the full dose of selumetinib[58][37][59].

Solid tumours

Phase I the maximum tolerated dose (MTD) of selumetinib, when combined with docetaxel and granulocyte colony stimulating factors in heavily pretreated patients with solid tumours, was 75mg twice daily in a phase I trial. The recommended phase II dose of selumetinib was 75mg twice daily when combined with docetaxel, without granulocyte colony stimulating factors, in less heavily pretreated patients. Docetaxel was administered as a 75 mg/m^2 intravenous infusion over 60 mins on day 1 of each 21-day cycle; oral selumetinib capsules were administered from day 3 onward. In Part A of the study, 22 patients with solid tumours received docetaxel plus selumetinib 50mg or 75mg twice daily (cohorts 1 and 2) or docetaxel plus granulocyte colony stimulating factors plus selumetinib 75mg twice daily (cohort 3); 18 patients were evaluable for dose-limiting toxicity (six patients in each cohort). The mean number of prior chemotherapy treatments was 3 in cohort 1 and ≥5 in cohorts 2 and 3. In Part B, 13 patients received selumetinib 75mg twice daily plus docetaxel without granulocyte colony stimulating factors; the mean number of prior chemotherapy treatments was 3. In Part A, cohort 2, the MTD was exceeded; dose-limiting toxicities (DLTs) were noted (grade 4 neutropenia [n = 2] and febrile neutropenia [n = 1]). No DLTs were reported in cohorts 1 and 3 of Part A. In Part B, grade 4 adverse events were noted in two patients (neutropenia [n = 1], febrile neutropenia [n = 1]). Combining Parts A and B, the most common adverse events (≥40% frequency) were peripheral oedema, diarrhoea, fatigue, nausea, vomiting, neutropenia and dermatitis acneiform. There was one death (pneumonia and febrile neutropenia, considered not to be study drug-related) and two permanent treatment discontinuations because of multiple adverse events[84].

Oral selumetinib (50, 100 and 200mg bid for 28-day cycles) was well tolerated in 23 patients with refractory solid tumours. The most frequently reported adverse events were rash, fatigue, diarrhoea, nausea, peripheral oedema, vomiting, taste perversion, hypoxia and blurred vision. In a part A of this dose-ascending study, dose-limiting toxicities included hypoxia (n = 1) at a dose of 200mg, and diarrhoea (1) and rash (1) after a dose of 300mg. The maximum tolerated dose was established to be 200mg bid[107].

In part B of the phase I trial 100 mg dose of selumetinib proved to be more tolerable than the 200mg dose over prolonged periods. Adverse events experienced were similar to part A, with elevated liver enzymes also noted. The 100mg dose has been chosen for phase II studies[32].

Acute myeloid leukaemia

Phase II in 42/47 patients with relapsed/refractory acute myeloid leukaemia (AML) receiving oral selumetinib at 100mg twice daily without interruption with cycles repeated every 28 days, treatment was tolerable. In this first phase II, multicentre clinical study in patients with advanced AML, the most frequently reported drug-related toxicities included grade 1/2 diarrhoea, nausea, and vomiting in 43%, 36%, 31% and 24% of patients, respectively. Grade 3/4 adverse events possibly related to treatment were fatigue, nausea and dehydration in 7%, 5% and 5% of patients, respectively[6].

Pharmacodynamics

Summary

Clinical studies In a phase Ib trial of selumetinib, pERK protein was reduced by 77% as determined by pre- and post-biopsy tissue testing from patients with solid tumours. The trough plasma concentration of selumetinib (400 ng/mL) led to a 35-44% inhibition of pERK. Of the 20 biopsies evaluable for cell proliferation marker, Ki-67, 9 patients had a reduction in Ki-67, with 5 patients demonstrating a reduction of ≤50%[31][32].

In a phase I study of selumetinib (25, 50, 75 or 100mg bid), PET scans with 3'-deoxy'-3'-[18F] flurothymidine (18F-FLT), a surrogate marker for proliferation, showed a qualitative and quantitative decrease in FLT uptake in tumours in one patient with melanoma compared with baseline. This was followed by a decrease in the RESIST criteria of 11% at the CT scan after 8 weeks. However, at the second CT scan, the patient showed progressive disease. The data in other 3 patients were inconclusive and warranted further investigation of 18F-FLT-PET scans as early predictors for patients on therapy with selumetinib[104].

Preclinical studies

Monotherapy Selumetinib inhibited the proliferation of several human cancer cell lines *in vitro*. *In vivo*, in several tumour xenograft models in mice including human colon and pancreatic carcinoma models, anti-tumour activity was shown which correlated with decreased ERK phosphorylation[111]. In addition, the compound showed anti-tumour properties in re-established tumours suggesting that the tumours maintained sensitivity to selumetinib after a treatment-free period[112].

Selumetinib was shown to specifically target cells with activated MEK from either Ras or B-Raf mutations, but not normal cells[110]. Further in vitro studies showed the compound is a highly specific inhibitor of MEK1/2[109].

Selumetinib (25 mg/kg, bid) in combination with gefitinib (75 mg/kg, qd) inhibited by 75.1% tumour growth in the LoVo human colorectal cancer xenograft murine model carrying a mutant *K-ras* allele. The cytostatic effect produced by combination of selumetinib and gefitinib was greater than monotherapies with each agent alone (42.2% and 34.5%, respectively, all compared with controls). *Ex vivo* tumour pharmacodynamic analysis of EGFR (epidermal growth factor receptor) and ERK1/2 MARK (extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase) phosphorylation by gefitinib and selumetinib, respectively, indicated that their enhanced antitumour activity was associated with dual inhibition of the ERK1/2 and EGFR pathways, and was observed only in tissue from animals receiving combination treatment[108].

In vivo xenograft models using mKRAS human tumour cell lines (NCT-116, CaLu-6, SW620) selumetinib in combination with either docetaxel, irinotecan, gemcitabine or temozolomide showed enhanced anti-tumour efficacy compared with single agent treatments. In HCT116 xenograft, a dosing regimen comprising docetaxel followed by selumetinib was more efficacious than a regimen with selumetinib dosed before docetaxel[113].

Similarly, the combination of selumetinib with vorinostat resulted in synergistic inhibition of proliferation of colorectal cancer cell lines *in vitro,* including those previously resistant to either drug alone (SW480 cells). The vorinostat-associated increase in phospho-ERK levels is thought to be involved in sensitising the cells to selumetinib[103].

Selumetinib inhibited tumour growth and metastasis with efficacy superior to paclitaxel in two distinct K-ras mutant orthotopic human non-small cell lung cancer (NSCLC) models in mice. Selumetinib reduced microvessel density and tumour cell proliferation and increased apoptosis without affecting the VEGFR2 expression. Moreover, the combined antitumour effects of selumetinib and cediranib resulted in a near complete metastasis suppression[100].

Combination therapy Preclinical data of selumetinib plus barasertib, administered in either sequence, showed greater antitumour activity than vehicle arms. Selutinib, when administered after barasertib, was more superior in inducing apoptosis and inhibiting tumour growth compared with monotherapy with either agent. In the study, nude mice bearing human non-small cell lung cancer tumour xenografts were dosed barasertib (150mg/kg/day SC for two days) or selumetinib (25 mg/kg/BID PO) as monotherapy and as combination therapy (dosed in sequence - selumetinib followed by barasertib or barasertib followed by selumetinib)[101].

Drug Interactions

Summary

Combination therapy with selumetinib and docetaxel did not affect the pharmacokinetics of either drug in a phase I trial. Docetaxel was administered as a 75 mg/m^2 intravenous infusion over 60 mins on day 1 of each 21-day cycle; oral selumetinib capsules were administered from day 3 onward. In Part A of the study, 22 patients with solid tumours received docetaxel plus selumetinib 50mg or 75mg twice daily (cohorts 1 and 2) or docetaxel plus granulocyte colony stimulating factors plus selumetinib 75mg twice daily (cohort 3); 18 patients were evaluable for dose-limiting toxicity (six patients in each cohort). In Part B, 13 patients received selumetinib 75mg twice daily plus docetaxel without granulocyte colony stimulating factors. Median total exposure to selumetinib was 130 days[84].

Therapeutic Trials

Biliary cancer

Phase II Interim data from a phase II study of selumetinib in patients with advanced biliary cancer have shown that the drug displayed very promising activity. The study was conducted at four institutions in the US. Patients received oral selumetinib (100mg bid) on a daily basis. A total of 29 patients completed accrual into the study; 25 patients were evaluable for the primary endpoint (i.e. overall response rate). Thirty-nine percent of patients had received one prior therapy. As at 15 January 2009, 22 patients were assessable for response and survival with three responders (one complete response; two partial responses), 14 patients had stable disease and five patients had progressive disease (PD). The tumour growth control rate (TGCR) was 77%. Median progression free survival was 7 months and median overall survival was 8.2 months. Immunohistochemistry results showed that none of the evaluable patients with PD (n = 3) had evidence of tumour phosphorylated

ERK (pERK) staining, whereas 90% of patients with tumour growth control (n = 15) had evidence staining with scores ranging from 1-3. Phosphorylated AKT (pAKT) did not correlate with response[102].

Glioma/Astrocytoma Interim results from a phase I trial showed that, administration of selumetinib resulted in a partial response in 11 of 18 paediatric patients (61%) with neurofibromatosis. Tumour shrinkage was maintained long term, for approximately two years, and as of early 2016, no disease progression had been observed in any trial participant. Patients remained on study for as long as four years[114][64][38].

Malignant melanoma

Phase II Chemotherapy-naive patients with advanced melanoma were randomised 1:1 to selumetinib (100 mg BD continuously) or temozolomide (200 mg/m^2 for 5 days, q28d). Patients randomised to temozolomide could receive selumetinib after disease progression. A total of 104 and 96 patients were randomised to selumetinib and temozolomide respectively. To date, 146 patients have their mutation staus confirmed; 67 were BRAF+ and 24 NRAS+. Of the non-uveal patients, 50% were BRAF+ and 68% were either BRAF+ or NRAS+. For progression-free survival, there was no difference between the two treatment arms in the overall population (151 events; HR 1.07; 80% ci 0.86,1.34) or in the BRAF+ subgroup (HR 0.85; 80% CI 0.58, 1.24). Overall survival data are immature (67 deaths) but the interim analysis showed no difference between the two arms in the overall population (HR 1.23; 80% CI 0.88, 1.71). In BRAF+ patients (25 deaths) the HR estimate for overall survival favoured selumetinib (HR 0.68; 80% CI 0.38, 1.21). Six patients receiving selumetinib had a confirmed partial response, of which 5 were BRAF+ (12% of BRAF+ patients). Nine patients receiving temozolomide had a confirmed partial response, 3 of which were BRAF+ (12% of BRAF+ patients)[106].

Non-small cell lung cancer (NSCLC)

Phase III Results from the phase III SELECT-1 trial demonstrated that selumetinib in combination with docetaxel did not significantly improve progression-free survival (PFS), overall survival (OS) or overall response rate (ORR), as compared to placebo + docetaxel as 88% patients had disease progression. Median PFS was 3.9 months and 2.8 months for selumetinib in combination with docetaxel and placebo + docetaxel, respectively (HR 0.93; 95% CI: 0.77,1.12; 2-sided p = 0.44). Median OS was 8.7 months and 7.9 months for selumetinib in combination and placebo + docetaxel, respectively (HR 1.05, 95% CI: 0.85, 1.30; 2-sided p = 0.64). ORR was 20.1 and 13.7 for selumetinib in combination and placebo + docetaxel, respectively (odds ratio: 1.61; 95% CI: 1.00, 2.62; 2-sided p = 0.051). Mean (SD) actual dose intensity relative to intended dose intensity of docetaxel over 6 cycles was similar between groups: 86.7% (15.90) with selumetinib in combination with docetaxel and 90.3% (15.01) with placebo + docetaxel[40].

Phase II In a phase II trial, although selumetinib demonstrated anti-tumour activity in patients with NSCLC, there was no difference observed between selumetinib and pemetrexed in the primary disease progression endpoint[54].

Results from a randomised phase II trial have demonstrated a greater increase in overall survival (primary endpoint) in 87 patients with KRAS-mutant NSCLC treated with selumetinib plus docetaxel, compared with docetaxel alone (9.4 months vs 5.2 months, respectively). However, the between treatment group in the primary endpoint was not significant. Secondary endpoints such as response rate (37% vs 0%, respectively) and progression-free survival (5.3 months vs 2.1 months, respectively), were significantly improved for selumetinib in combination with docetaxel versus docetaxel alone[49][50].

Phase I: According to results from a phase I trial in 55 evaluable patients, 11 patients (20%) and 9 patients (16%) showed confirmed and unconfirmed partial responses respectively, while 21 patients (38%) had stable disease (≥6 weeks). Earlier, in the same trial, stable disease, partial response and unconfirmed partial response was observed in 6, 4 and 7 patients, respectively, for at least six weeks. These preliminary data were from 20 patients, who were available for evaluation at the time of reporting these data. These patients were not treated with the full dose of selumetinib[58][37][59].

Results from the phase Ib TATTON trial demonstrated that, mereletinib was well tolerated in patients with EGFR mutation positive non-small cell lung cancer. The most common adverse events observed in 71 patients were diarrhoea, vomiting, anaemia, constipation, cough and nausea with mereletinib and durvalumab group; diarrhoea, nausea and fatigue with mereletinib and selumetinib group; and vomiting, nausea and rash with mereletinib and savolitinib group[57].

Metastatic colorectal cancer

Phase II In an exploratory trial comparing selumetinib with capecitabine in 69 patients who had previously failed 1-2 chemotherapy regimes, no significant differences in efficacy were observed. 82% of patients receiving selumetinib (100 mg bid) and 80% of those receiving capecitabine (1250 mg/m^2 bid) had progression events. Median progression free survival was 81 days and 88 days for selumetinib and capecitabine respectively[16].

Phase I In The phase Ib study, One patient maintained stable disease for over 9 months. In the in the escalation cohort**,** disease control rate was 56 %. The data was reported from 18 metastatic colorectal cancer patients treated with the combination selumetinib and cyclosporin A[13][14].

Solid tumours

Phase II Treatment with selumetinib at 100mg twice daily in 4-week cycle in 52 women with low-grade serous ovarian or peritoneal cancer resulted in disease control in 81%, defined as either complete or partial response or progression-free survival or progression-free survival of >6 months. In this phase II trial, sponsored by the National Cancer Institute in collaboration with the Gynaecologic Oncology Group, eight patients showed complete response and seven patients had partial response The median survival rate without cancer progression was 11 months[89].

Phase I Therapeutic responses were noted in 5 of 28 (18%) pretreated patients with solid tumours who received selumetinib 75mg twice daily plus docetaxel, with or without granulocyte colony stimulating factors, in a phase I trial[84].

In 23 patients with refractory solid tumours, the best clinical response after oral selumetinib (50-300mg bid for 28-day cycles) was stable disease. In part A of this dose-ascending study, four patients (3/7 with melanoma and 1/1 with non-small cell lung cancer) remained on the study for >4 cycles, and two patients with melanoma for 8 and 10 cycles, respectively[107].

In part B of the phase I trial, 19 patients with tumours of various types had stable disease at 2 months and 9 of those had stable disease at ≥5 months. For patients in the trial with melanoma, 12 had stable disease at 2 months and 6 patients at ≥5 months. Patients were randomised to recieve 100 or 200mg doses of selumetinib, twice a day for 28 days[31].

Acute myeloid leukaemia

Phase II In 47 patients with relapsed/refractory acute myeloid leukaemia (AML) receiving oral selumetinib at 100mg twice daily without interruption with cycles repeated every 28 days, four patients had minor response (defined as >50% decline in peripheral blood and/or marrow blasts lasting 4 weeks). Additionally, two patients also had >50% decline in marrow blasts but did not have a follow-up confirmatory biopsy. In this first phase II, multicentre clinical study in patients with advanced AML, six additional patients displayed evidence of disease stabilisation for a median of 34 days[6].

Development History

Event Date	Update Type	Comment
01 Feb 2017	Trial Update	The National Cancer Institute plans a phase II trial for Pancreatic cancer (Late-stage disease, Metastatic disease, Monotherapy) in USA (PO) (NCT03040986) Updated 07 Feb 2017
20 Dec 2016	Trial Update	University of Texas M.D. Anderson Cancer Center plans a phase II trial for Non-small cell lung cancer (Combination therapy, Metastatic disease, Late-stage disease) in USA (NCT03004105) Updated 02 Jan 2017
17 Nov 2016	Phase Change - Discontinued(III)	Discontinued - Phase-III for KRAS mutation-positive Non-small cell lung cancer (Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater) in Austria, Brazil, Canada, United Kingdom, Sweden, Italy, Israel, France, Australia, USA, Poland, Netherlands, Hungary, Germany, Spain, Romania, Belgium, Turkey, Chile, Argentina, Bulgaria, Portugal, Peru, Russia, Mexico, Ukraine (PO) because of unfavourable safety and efficacy results (before November 2016; AstraZeneca pipeline, November 2016) Updated 17 Nov 2016
07 Oct 2016	Scientific Update	Safety and efficacy results from the SELECT-1 trial presented at the 41st European Society for Medical Oncology Congress (ESMO-2016) [40] Updated 07 Dec 2016
07 Oct 2016	Scientific Update	Efficacy and adverse events data from a phase I trial in Non-small cell lung cancer (First-line therapy, Combination therapy, Late-stage disease) presented at the 41st European Society for Medical Oncology Congress (ESMO-2016) [58] Updated 06 Dec 2016
01 Oct 2016	Trial Update	AstraZeneca completes the phase III SUMIT trial in Uveal Melanoma in USA, Belgium, Canada, Czech Republic, Finland, France, Germany, Israel, Netherlands, Spain and United Kingdom (NCT01974752) Updated 20 Jan 2017
14 Sep 2016	Financial Update	Credit Suisse financial data update Updated 12 Nov 2016
20 Jul 2016	Trial Update	The National Cancer Institute plans to initiate a pilot clinical trial for Neurofibromatosis in USA (PO) (NCT02839720) Updated 25 Jul 2016
01 Jun 2016	Trial Update	AstraZeneca completes its phase IIa trial for Non-small cell lung cancer (Combination therapy, Late-stage disease) in USA (NCT02179671) Updated 05 Aug 2016
31 May 2016	Trial Update	AstraZeneca discontinues a phase I trial in Biliary cancer (Inoperable/Unresectable, metastatic disease, in combination with cisplatin and gemcitabine) in Japan due to change in the development strategy (NCT01949870) Updated 01 Jun 2016

12 May 2016	Regulatory Status	Selumetinib receives Orphan Drug status for Thyroid cancer in USA [75] Updated 12 May 2016
16 Apr 2016	Scientific Update	Preliminary adverse events and efficacy data from a phase Ib trial in Colorectal cancer (Combination therapy, Late-stage disease, Metastatic disease) presented at the 107th Annual Meeting of the American Association for Cancer Research [13] Updated 19 Jul 2016
23 Mar 2016	Phase Change - II	Phase-II clinical trials in Colorectal cancer (Second-line therapy or greater, Metastatic disease, Late-stage disease) in Netherlands (PO) (EudraCT2014-003811-13) Updated 15 Feb 2017
23 Mar 2016	Phase Change - II	Phase-II clinical trials in Non-small cell lung cancer (Second-line therapy or greater, Late-stage disease, Metastatic disease) in Netherlands (PO) (EudraCT2014-003811-13) Updated 15 Feb 2017
15 Mar 2016	Biomarker Update	Biomarkers information updated Updated 29 Sep 2016
22 Feb 2016	Trial Update	Russian Academy of Medical Sciences plans a phase II trial for Breast cancer (Neoadjuvant therapy, Late-stage disease, Metastatic disease) in Russia (NCT02685657) Updated 22 Feb 2016
01 Jan 2016	Trial Update	AstraZeneca completes enrolment in the SELECT-1 trial for Non-small cell lung cancer (Metastatic disease, Second-line therapy or greater, Combination therapy, Late-stage disease) (PO) [40] Updated 07 Dec 2016
01 Jan 2016	Trial Update	AstraZeneca completes a phase I trial for Non-small cell lung cancer (First-line therapy, Combination therapy, Late-stage disease) in United Kingdom (NCT01809210) Updated 17 Mar 2016
31 Dec 2015	Trial Update	National Cancer Institute initiates enrolment in a phase II trial for Neurofibromatosis (Inoperable) in USA (NCT02644512) Updated 08 Jan 2016
01 Dec 2015	Trial Update	AstraZeneca initiates enrolment in a phase I trial for Solid tumours (Combination therapy, Late-stage disease, metastatic disease) in USA (NCT02586987) Updated 20 Jan 2016
30 Oct 2015	Trial Update	AstraZeneca plans a phase I trial for Solid tumours (Late stage disease) in USA (NCT02586987) Updated 30 Oct 2015
01 Oct 2015	Trial Update	AstraZeneca completes enrolment in its phase IIa trial for Non-small cell lung cancer (Combination therapy, Late-stage disease) in USA (NCT02179671) Updated 08 Oct 2015

24 Jul 2015	Trial Update	OHSU Knight Cancer Institute and National Cancer Institute plan a phase I trial in Non-small cell lung cancer (Combination therapy, Second-line therapy or greater, Late-stage disease, Metastatic disease) in USA (NCT02503358) Updated 24 Jul 2015
30 Jun 2015	Phase Change - Discontinued(II)	Discontinued - Phase-II for Uveal melanoma (Combination therapy, Monotherapy, Second-line therapy or greater) in United Kingdom (PO) Updated 11 Dec 2015
30 Jun 2015	Phase Change - Discontinued(III)	Discontinued - Phase-III for Uveal melanoma (Combination therapy, First-line therapy, Metastatic disease) in USA, Canada, France, Israel, Germany, Spain, Czech Republic, Finland, Netherlands, Belgium and United Kingdom (PO) Updated 06 Oct 2015
22 Jun 2015	Phase Change - No development reported(II)	No recent reports on development identified - Phase-II for Biliary cancer (Inoperable/Unresectable) in USA (PO) Updated 22 Jun 2015
22 Jun 2015	Phase Change - No development reported(II)	No recent reports on development identified - Phase-II for Colorectal cancer (Metastatic disease, Second-line therapy or greater) in Brazil (PO) Updated 22 Jun 2015
22 Jun 2015	Phase Change - No development reported(II)	No recent reports on development identified - Phase-II for Non-small cell lung cancer (Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater) in Czech Republic and Denmark (PO) Updated 22 Jun 2015
18 Jun 2015	Active Status Review	Selumetinib is still in phase II trials for Colorectal cancer (Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater) in USA Updated 22 Jun 2015
30 May 2015	Scientific Update	Adverse events data from the TATTON phase Ib trial in Non-small cell lung cancer (Combination therapy, Second-line therapy or greater, Late-stage disease, Metastatic disease) presented at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO-2015) [57] Updated 02 Jul 2015
06 May 2015	Active Status Review	Selumetinib is still in phase II trials for Thyroid cancer (Monotherapy) in USA and Canada Updated 22 Jun 2015
04 May 2015	Trial Update	AstraZeneca completes enrolment in the SUMIT trial for Uveal melanoma (Combination therapy, First-line therapy, Metastatic disease) in USA, United Kingdom, Belgium, Canada, Czech Republic, Finland, France, Germany, Israel, the Netherlands and Spain (NCT01974752) Updated 11 Jun 2015
01 May 2015	Trial Update	AstraZeneca completes a phase I trial (combination therapy, second-line therapy) for Non-small cell lung cancer in Japan (NCT01605916) Updated 29 Jun 2015

01 May 2015	Phase Change - II	Phase-II clinical trials in Neurofibromatosis (In adults, Inoperable/Unresectable) in USA (PO) (NCT02407405) Updated 12 Jun 2015
17 Apr 2015	Regulatory Status	Selumetinib receives Orphan Drug status for Uveal melanoma in USA Updated 20 Apr 2015
15 Apr 2015	Trial Update	National Cancer Centre (Singapore) terminates phase II portion of phase I/II trial in Hepatocellular carcinoma (Combination therapy, Late-stage disease, first-line therapy) in Singapore (NCT01029418) Updated 28 May 2015
08 Apr 2015	Phase Change - II	Phase-II clinical trials in Uveal melanoma (Monotherapy, Combination therapy, Second-line therapy or greater) in United Kingdom (PO) Updated 11 Dec 2015
01 Apr 2015	Trial Update	AstraZeneca initiates enrolment in a phase I bioavailability trial for Healthy volunteers in the United Kingdom (NCT02322749) Updated 14 Jul 2015
31 Mar 2015	Active Status Review	Selumetinib is still in phase III trials for Non-small cell lung cancer (Combination therapy, Late-stage disease, Metastatic disease, Second-line therapy or greater), Thyroid cancer (Combination therapy) and Uveal melanoma (Combination therapy, First-line therapy, Metastatic disease) in countries worldwide Updated 22 Jun 2015
31 Mar 2015	Phase Change - Discontinued(II)	Discontinued - Phase-II for Acute myeloid leukaemia (Recurrent) and Multiple myeloma in USA prior to March 2015 (PO) Updated 22 Jun 2015
31 Mar 2015	Phase Change - Discontinued(II)	Discontinued - Phase-II for Malignant melanoma (Combination therapy, First-line therapy) in USA, Brazil, Czech Republic, France, Germany, Hungary, Netherlands, Norway, Spain, Sweden, Switzerland and United Kingdom prior to March 2015 (PO) Updated 22 Jun 2015
31 Mar 2015	Phase Change - Discontinued(II)	Discontinued - Phase-II for Pancreatic cancer (Late-stage disease, Metastatic disease, Second-line therapy or greater, Monotherapy) in USA, Australia, Bulgaria, Hungary and Romania prior to March 2015 (PO) Updated 22 Jun 2015
01 Feb 2015	Phase Change - II	Phase-II clinical trials in Thyroid cancer (Late-stage disease, Second-line therapy or greater) in United Kingdom (PO) (ISRCTN17468602; EudraCT2015-002269-47) Updated 10 Mar 2016
01 Feb 2015	Trial Update	AstraZeneca initiates a phase II trial (Combination therapy, Second-line therapy or greater, Metastatic disease, Late-stage disease) for Non-small cell lung cancer in Canada (NCT02337530) Updated 01 Jul 2015

01 Feb 2015	Trial Update	AstraZeneca initiates enrolment in a phase I bioavailability trial for Healthy volunteers in the United Kingdom (NCT02322749) Updated 26 Feb 2015
14 Jan 2015	Trial Update	Netherlands Cancer Institute initiates enrolment in phase I/II trial for Colorectal, Non-small cell and Pancreatic cancer (Late-stage disease, Second-line therapy or greater) in Netherlands (EudraCT2014-001855-22) Updated 11 Feb 2015
31 Dec 2014	Active Status Review	Selumetinib is still in preclinical trials for Pancreatic cancer (Combination therapy) in United Kingdom Updated 22 Jun 2015
30 Dec 2014	Trial Update	AstraZeneca plans a phase I bioavailability trial in Healthy volunteers in the United Kingdom (NCT02322749) Updated 30 Dec 2014
04 Nov 2014	Scientific Update	Preliminary efficacy and adverse events data from a phase I trial in non-small cell lung cancer (late-stage disease, combination therapy) presented at the 39th Congress of the European Society of Medical Oncology (ESMO-2014) [37] Updated 24 Nov 2014
04 Nov 2014	Phase Change - III	Phase-III clinical trials in Thyroid cancer (Combination therapy) in Brazil (PO) before November 2014 Updated 23 Nov 2014
01 Nov 2014	Phase Change - II	Phase-II clinical trials in Biliary cancer (Combination therapy, Late-stage disease, Metastatic disease) in Canada (PO) (NCT02151084) Updated 10 Dec 2014
01 Nov 2014	Trial Update	AstraZeneca completes a phase I trial in healthy volunteers and patients with Hepatic impairment in USA (NCT02063230) Updated 10 Dec 2014
30 Oct 2014	Trial Update	AstraZeneca completes a phase I bioavailability trial in Healthy volunteers in United Kingdom (NCT02238782) Updated 03 Dec 2014
15 Oct 2014	Trial Update	A phase II trial is planned in Non small cell lung cancer (Combination therapy, Metastatic disease) in Canada (I219) Updated 15 Oct 2014
01 Oct 2014	Trial Update	AstraZeneca initiates enrolment in a phase I bioavailability trial in Healthy volunteers in the UK (NCT02238782) Updated 22 Oct 2014
18 Aug 2014	Trial Update	AstraZeneca completes a phase I trial in Healthy volunteers in USA (NCT02056392) Updated 15 Sep 2014
01 Aug 2014	Phase Change - I	Phase-I clinical trials in Non-small cell lung cancer (Combination therapy, Late-stage disease, Second-line therapy or greater) in Taiwan and South Korea (PO) (NCT02143466) Updated 12 Jun 2015

01 Aug 2014	Trial Update	AstraZeneca initiates enrolment in the TATTON trial for Non-small cell lung cancer (Combination therapy, Late-stage disease, Second-line therapy or greater) in USA and Japan (PO) (NCT02143466) Updated 12 Jun 2015
01 Aug 2014	Trial Update	National Cancer Institute initiates enrolment in a phase I trial for Solid tumours (Metastatic disease, Combination therapy) in USA (NCT02188264) Updated 26 Aug 2014
01 Jul 2014	Trial Update	AstraZeneca initiates enrolment in a phase II trial for Non-small cell lung cancer (Late-stage disease, Metastatic disease, Combination therapy) in USA (NCT02179671) Updated 19 Feb 2015
01 Jul 2014	Trial Update	AstraZeneca and Merck & Co complete a phase I trial for Solid tumours (Combination therapy, Late-stage disease, Second-line or greater therapy, Metastatic disease) in the USA and United Kingdom (NCT01021748) Updated 09 Sep 2014
01 Jul 2014	Trial Update	AstraZeneca completes a phase I trial in healthy volunteers and patients with renal impairment in USA (NCT02063204) Updated 02 Sep 2014
30 Jun 2014	Trial Update	AstraZeneca completes a phase I drug-interaction trial in Healthy volunteers in USA (NCT02093728) Updated 24 Sep 2014
02 Jun 2014	Scientific Update	Interim efficacy and adverse event data from a phase I trial in Neurofibromatoses presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO-2014) [64] Updated 16 Jun 2014
29 May 2014	Trial Update	University Health Network, Toronto, plans a phase II trial for Biliary cancer (combination therapy; late-stage disease) in Canada (NCT02151084) Updated 10 Jun 2014
01 May 2014	Trial Update	AstraZeneca completes a phase I trial in Healthy volunteers in United Kingdom (NCT01960374) Updated 23 Jul 2014
28 Apr 2014	Trial Update	AstraZeneca completes a phase I trial in Healthy volunteers in USA (NCT02046850) Updated 01 May 2014
02 Apr 2014	Phase Change - III	Phase-III clinical trials in Thyroid cancer (in combination with radioactive iodine) in USA, Denmark, France, Germany, Italy, Poland and Sweden (PO) Updated 20 May 2014
01 Apr 2014	Phase Change - III	Phase-III clinical trials in Uveal melanoma (Combination therapy, First-line therapy, Metastatic disease) in USA (PO) (NCT01974752) Updated 24 Jul 2015

01 Apr 2014	Phase Change - III	Phase-III clinical trials in Uveal melanoma (Combination therapy, First-line therapy, Metastatic disease) in Spain, Israel, Germany, Finland, Czech Republic, Canada, Belgium (PO) after April 2014 (NCT01974752) Updated 11 Jun 2015
01 Apr 2014	Trial Update	AstraZeneca initiates a phase I pharmacokinetics trial in healthy male volunteers in USA (NCT02093728) Updated 18 Jun 2014
01 Apr 2014	Phase Change - III	Phase-III clinical trials in Uveal melanoma (combination therapy, first-line therapy, metastatic disease) in United Kingdom, France and Netherlands (PO) Updated 20 May 2014
31 Mar 2014	Trial Update	AstraZeneca initiates a phase I trial in healthy volunteers and patients with renal impairment in USA (NCT02063204) Updated 03 Jun 2014
28 Mar 2014	Trial Update	AstraZeneca plans a phase I pharmacokinetics trial in healthy male volunteers in USA (NCT02093728) Updated 28 Mar 2014
01 Mar 2014	Trial Update	AstraZeneca initiates enrolment in a phase I trial in Healthy volunteers in USA (NCT02056392) Updated 16 Jun 2014
01 Mar 2014	Trial Update	AstraZeneca initiates a phase I trial in healthy volunteers and patients with hepatic impairment in USA (NCT02063230) Updated 11 Jun 2014
28 Feb 2014	Trial Update	AstraZeneca completes a phase I pharmacokinetics trial in healthy volunteers in the USA (NCT01974349) Updated 07 Apr 2014
24 Feb 2014	Trial Update	AstraZeneca initiates a phase I pharmacokinetics trial in healthy volunteers in the US (NCT02046850) Updated 27 Feb 2014
13 Feb 2014	Trial Update	AstraZeneca plans phase I trials in healthy volunteers and patients with renal or hepatic impairment in the USA (NCT02063204; NCT02063230) Updated 27 Feb 2014
12 Feb 2014	Phase Change - II	Phase-II clinical trials in Uveal melanoma (combination therapy, first-line therapy, metastatic disease) in United Kingdom (PO) Updated 31 Mar 2014
11 Feb 2014	Trial Update	AstraZeneca resumes enrolment in a phase II trial in Non-small cell lung cancer (second-line therapy or greater, late-stage disease) in the US, France, Germany and Hungary (NCT01750281) Updated 25 Mar 2014
05 Feb 2014	Trial Update	AstraZeneca plans a phase I trial in healthy volunteers in the USA (NCT02056392) Updated 11 Feb 2014
31 Jan 2014	Trial Update	AstraZeneca plans the phase II SUMIT trial in Uveal melanoma (combination therapy, metastatic disease) in the USA, the EU and Israel (NCT01974752) Updated 11 Feb 2014

24 Jan 2014	Trial Update	AstraZeneca plans a phase I pharmacokinetics trial in Healthy volunteers in the US (NCT02046850) Updated 18 Feb 2014
30 Nov 2013	Trial Update	AstraZeneca initiates a phase I trial to investigate the effect of food on the pharmacokinetics of selumetinib in healthy volunteers in USA (NCT01974349) Updated 06 Jan 2014
14 Nov 2013	Trial Update	AstraZeneca plans the phase II SUMIT trial for Uveal melanoma (combination therapy, metastatic disease) in USA, European Union and Israel (NCT01974752) Updated 14 Nov 2013
01 Nov 2013	Trial Update	AstraZeneca completes a phase I pharmacokinetics trial in healthy volunteers in the United Kingdom (NCT01931761) Updated 23 Dec 2013
10 Oct 2013	Financial Update	Credit Suisse financial data update Updated 12 Nov 2016
01 Oct 2013	Phase Change - I	Phase-I clinical trials in Biliary cancer (Inoperable/Unresectable, metastatic disease, in combination with cisplatin and gemcitabine) in Japan (PO) Updated 01 Dec 2014
12 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (combination therapy, metastatic disease, late-stage disease, second-line therapy or greater) in Argentina, Australia, Belgium, Chile, Israel, Italy and Portugal after September 2013 (PO) Updated 01 Apr 2014
12 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (combination therapy, late-stage disease, metastatic disease, second-line therapy or greater) in United Kingdom, Germany, Sweden, Poland, Austria & Spain (PO) Updated 06 Jan 2014
12 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (combination therapy, late-stage disease, metastatic disease, second-line therapy or greater) in Canada and in the Netherlands after September 2013 (PO) Updated 15 Nov 2013
12 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) in Hungary (PO) Updated 30 Sep 2013
01 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (Metastatic disease, Second-line therapy or greater, Combination therapy, Late-stage disease) in Brazil (PO) (NCT01933932) after September 2013 Updated 19 Feb 2015
01 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (Combination therapy, Second-line therapy or greater, Late-stage disease, Metastatic disease) in Mexico and Romania (PO) Updated 02 Sep 2014

01 Sep 2013	Phase Change - III	Phase-III clinical trials in Non-small cell lung cancer (metastatic disease, late-stage disease, combination therapy, second-line therapy or greater) in Bulgaria, France, Peru, Russia, Ukraine, Turkey and USA after September 2013 (PO) (NCT01933932) Updated 23 Jul 2014
30 Aug 2013	Trial Update	AstraZeneca suspends a phase II trial in Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) in Hungary & Germany (NCT01750281) Updated 06 Sep 2013
29 Aug 2013	Trial Update	AstraZeneca plans the global phase III SELECT-1 trial for Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) (NCT01933932) Updated 06 Sep 2013
09 Jul 2013	Company Involvement	AstraZeneca and the University of Cambridge and Cancer Research UK Cambridge Institute enter into a 2-year collaboration to advance cancer research and to evaluate investigational therapies, including selumetinib, in pancreatic cancer [1] Updated 18 Jul 2013
28 Jun 2013	Trial Update	AstraZeneca completes a phase II trial in Malignant melanoma (combination therapy, first-line therapy) in Brazil, Czech Republic, France, Germany, Hungary, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom and USA (NCT00936221) Updated 28 Jun 2013
03 Jun 2013	Trial Update	AstraZeneca plans to initiate a pivotal phase III trial for KRAS-mutant Non-small cell lung cancer (in combination with docetaxel) in USA [30] Updated 13 Jun 2013
23 May 2013	Phase Change - II	Phase-II clinical trials in Thyroid cancer (in combination with radioactive iodine) in Poland after May 2013 (PO) Updated 01 Apr 2014
23 May 2013	Phase Change - II	Phase-II clinical trials in Thyroid cancer (combination therapy with radioactive iodine) in Denmark, France, Germany, Italy and USA after May 2013 (PO) Updated 15 Nov 2013
23 May 2013	Phase Change - II	Phase-II clinical trials in Thyroid cancer (combination therapy) in Sweden (PO) Updated 30 May 2013
09 Apr 2013	Phase Change - I	Phase-I clinical trials in Non-small cell lung cancer (first line combination therapy, late-stage disease) in United Kingdom (PO) Updated 18 Apr 2013
31 Jan 2013	Phase Change - I	Phase-I clinical trials in Non-small cell lung cancer (combination first/second-line therapy, late-stage/metastatic disease) in Canada (PO) Updated 06 Sep 2013
10 Dec 2012	Phase Change - II	Phase-II clinical trials in Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) in Germany (PO) Updated 06 Sep 2013

01 Dec 2012	Trial Update	AstraZeneca initiates enrolment in a phase II trial for Non-small cell lung cancer (second-line treatment, combination therapy, late-stage & metastatic disease) in Hungary (NCT01750281) Updated 29 Jan 2013
07 Nov 2012	Trial Update	National Cancer Centre (Singapore) completes enrolment in its Phase-I/II trial for Hepatocellular carcinoma (combination therapy, first-line therapy, late-stage disease) in Singapore (NCT01029418) Updated 06 Dec 2012
31 Oct 2012	Trial Update	AstraZeneca completes a phase I trial in healthy volunteers in the USA (NCT01635023) Updated 11 Feb 2014
26 Oct 2012	Trial Update	AstraZeneca completes enrolment in its phase II trial for Non-small cell lung cancer (second-line therapy, combination therapy, late-stage & metastatic disease) in USA, Belgium, Brazil, Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Mexico, Peru and Spain (NCT00890825) Updated 29 Jan 2013
16 Jul 2012	Trial Update	AstraZeneca plans a phase I trial in healthy volunteers in USA (NCT01635023) Updated 16 Jul 2012
09 Jul 2012	Phase Change - Preclinical	Preclinical trials in Pancreatic cancer (combination therapy) in United Kingdom (PO) Updated 18 Jul 2013
14 Jun 2012	Phase Change - I	Phase-I clinical trials in Non-small cell lung cancer (combination, second-line therapy) in Japan (PO) Updated 02 Jul 2012
04 Jun 2012	Scientific Update	Efficacy and adverse events data from a phase II trial in Non-small cell lung cancer released by AstraZeneca [49] Updated 08 Jun 2012
21 May 2012	Trial Update	AstraZeneca plans a phase I trial (combination therapy, second-line therapy) for Non-small cell lung cancer in Japan (NCT01605916) Updated 13 Jun 2012
13 Apr 2012	Trial Update	AstraZeneca completes enrolment in its phase II trial for advanced or metastatic Colorectal cancer (second-line therapy) in the US (NCT01116271) Updated 23 Apr 2012
27 Dec 2011	Phase Change - II	Phase-II clinical trials in Malignant melanoma in Brazil (PO) Updated 13 Jan 2012
16 Nov 2011	Scientific Update	Interim efficacy, adverse events and drug interactions data from a Phase-I trial of combination therapy with docetaxel in Solid tumours presented at the 23rd AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2011) [84] Updated 30 Dec 2011

12 Oct 2011	Trial Update	AstraZeneca completes a phase II trial in Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) in USA, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Denmark, France, Hungary, Italy, Mexico, Peru & Spain (NCT00890825) Updated 12 Oct 2011
30 Sep 2011	Scientific Update	Topline efficacy data from a phase II trial in KRAS-mutant Non-small cell lung cancer released by Array BioPharma [50] Updated 04 Oct 2011
28 Jul 2011	Phase Change - II	Phase-II clinical trials in Solid tumours in USA (PO) Updated 02 Aug 2011
01 Jun 2011	Phase Change - I/II	Phase-I/II clinical trials in Astrocytoma (in children, adolescents and adults up to 21 years of age) in USA (PO) Updated 16 Jun 2014
01 Jun 2011	Trial Update	The National Cancer Institute initiates enrolment in a phase I/II trial for Glioma and Astrocytoma in USA (NCT01386450) Updated 16 Jun 2014
01 Jun 2011	Trial Update	National Cancer Institute (USA) terminates Phase-II trial in Hepatocellular carcinoma (first-line therapy, late-stage disease, monotherapy) in USA (NCT00604721) Updated 06 Dec 2012
01 May 2011	Phase Change - I	Phase-I clinical trials in Neurofibromatosis (in children and adolescents) in USA (PO) Updated 16 Jun 2014
06 Apr 2011	Scientific Update	Pharmacodynamics data from a preclinical study in Cancer presented at the 102nd Annual Meeting of the American Association for Cancer Research (102nd-AACR-2011) [100] Updated 21 Apr 2011
31 Mar 2011	Trial Update	AstaZeneca completes enrolment in its Phase-I trial for Solid tumours (combination therapy with standard chemotherapies, late-stage disease) in the USA (NCT00600496) Updated 27 Apr 2011
30 Sep 2010	Trial Update	The National Cancer Institute initiates enrolment in a phase II trial (NCT01229150) for Non-small cell lung cancer in USA Updated 11 Nov 2010
26 Jul 2010	Trial Update	AstraZeneca completes enrolment in its phase II trial for KRAS mutation positive non-small cell lung cancer in USA, Belgium, Brazil, Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Mexico, Peru and Spain (NCT00890825) Updated 12 Aug 2010
30 Apr 2010	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Colorectal cancer (second-line therapy, in combination with irinotecan) in USA (PO) Updated 17 May 2010

21 Apr 2010	Scientific Update	Preclinical pharmacodynamics data in Non-small cell lung cancer (in combination with barasertib) presented at the 101st Annual Meeting of the American Association for Cancer Research (AACR-2010) [101] Updated 27 Apr 2010
01 Apr 2010	Phase Change - I/II	Phase-I/II clinical trials in Glioma (in children, adolescents and adults up to 21 years of age) in USA (PO) Updated 16 Jun 2014
09 Mar 2010	Trial Update	AstraZeneca completes enrolment in its phase II trial for Malignant melanoma (first-line therapy in combination with dacarbazine) in USA, Czech Republic, France, Germany, Hungary, Netherlands, Norway, Spain, Sweden, Switzerland and United Kingdom (NCT00936221) Updated 18 Mar 2010
31 Dec 2009	Trial Update	AstraZeneca and Merck initiate enrolment in a phase I trial for Solid tumours (Combination therapy, Late-stage disease, Second-line or greater therapy) in the USA (NCT01021748) Updated 07 Jan 2010
08 Dec 2009	Scientific Update	Safety and efficacy data from a phase II trial in Acute myeloid leukaemia presented at the 51st Annual Meeting and Exposition of the American Society of Hematology (ASH-2009) [6] Updated 21 Jan 2010
01 Nov 2009	Phase Change - I	Phase-I clinical trials in Solid tumours (Combination therapy, Late-stage disease, Second-line therapy or greater) in United Kingdom (PO) (NCT01021748) Updated 09 Sep 2014
01 Nov 2009	Phase Change - I/II	Phase-I/II clinical trials in Hepatocellular carcinoma (combination therapy, first-line therapy, late-stage disease) in Singapore (PO) Updated 06 Dec 2012
16 Oct 2009	Trial Update	AstraZeneca initiates enrolment in a phase II trial in cancer patients with BRAF mutations in the US Updated 16 Mar 2010
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Czech Republic (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in France (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Germany (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Hungary (PO) Updated 15 Feb 2011

31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Netherlands (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Spain (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Sweden (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in United Kingdom (PO) Updated 15 Feb 2011
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Norway (PO) Updated 18 Mar 2010
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in Switzerland (PO) Updated 18 Mar 2010
31 Jul 2009	Phase Change - II	Phase-II clinical trials in Malignant melanoma (first-line therapy, in combination with dacarbazine) in USA (PO) Updated 16 Mar 2010
01 Jun 2009	Company Involvement	AstraZeneca and Merck collaborate on investigating combination regimen with selumetinib and MK 2206 for the treatment of solid tumours Updated 09 Jun 2009
19 May 2009	Phase Change - II	Phase-II clinical trials in Non-small cell lung cancer (combination second-line therapy, late-stage/metastatic disease) in Denmark (PO) Updated 06 Sep 2013
30 Apr 2009	Trial Update	AstraZeneca initiates a phase II trial (NCT00890825) of selumetinib capsules in combination with a docetaxel in Non-small cell lung cancer in North America and European Union Updated 31 May 2009
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Belgium (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Canada (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Czech Republic (PO) Updated 15 Feb 2011

29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Hungary (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Italy (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Mexico (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Peru (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Spain (PO) Updated 15 Feb 2011
29 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in Bulgaria (PO) Updated 15 Feb 2011
24 Apr 2009	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Non-small cell lung cancer (second-line therapy in combination with docetaxel) in France (PO) Updated 15 Feb 2011
22 Apr 2009	Scientific Update	Interim efficacy & adverse events data from a phase II trial in Biliary cancer presented at the 100th Annual Meeting of the American Association for Cancer Research (AACR-2009) [102] Updated 31 May 2009
04 Nov 2008	Trial Update	AstraZeneca completes a phase II trial in metastatic Colorectal cancer (second- or third-line therapy) in Brazil (NCT00514761) Updated 15 Feb 2011
04 Nov 2008	Trial Update	AstraZeneca completes a phase II trial in late-stage Non-small cell lung cancer (second- or third-line therapy) in USA, Bulgaria and Romania (NCT00372788) Updated 15 Feb 2011
24 Oct 2008	Scientific Update	Final pharmacodynamics data from two preclinical studies , [103] and one phase I study [104] in Cancer presented at the 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008) Updated 01 Dec 2008
16 Sep 2008	Scientific Update	Pharmacokinetics data from a phase I trial in patients with advanced cancer presented at the 33rd Congress of the European Society for Medical Oncology (ESMO-2008) [105] Updated 30 Sep 2008

03 Jun 2008	Scientific Update	Efficacy and adverse events data from a phase II trial in metastatic colorectal cancer presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008) [16] Updated 17 Jun 2008
03 Jun 2008	Scientific Update	Efficacy data from phase II trials in Malignant melanoma and non-small cell lung cancer presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008) [106], [54] Updated 16 Jun 2008
11 May 2008	Trial Update	AstraZeneca completes a phase II trial in late-stage or metastatic Pancreatic cancer (second-line therapy) in USA, Australia, Bulgaria, Hungary and Romania (NCT00372944) Updated 15 Feb 2011
06 May 2008	Phase Change - II	Phase-II clinical trials in Multiple myeloma in USA (PO) Updated 15 May 2008
31 Dec 2007	Trial Update	AstraZeneca initiates enrolment in a phase I trial for Solid tumours (combination therapy with standard chemotherapies, late-stage disease) in the USA (NCT00600496) Updated 27 Apr 2011
31 Dec 2007	Phase Change - II	Phase-II clinical trials in Acute myeloid leukaemia in USA (PO) Updated 15 May 2008
31 Dec 2007	Phase Change - II	Phase-II clinical trials in Ovarian cancer in USA (PO) Updated 15 May 2008
20 Dec 2007	Phase Change - Discontinued(II)	Discontinued - Phase-II for late-stage Malignant melanoma (first-line monotherapy) in World (PO) Updated 15 Feb 2011
01 Dec 2007	Phase Change - II	Phase-II clinical trials in Hepatocellular carcinoma (first-line therapy, late-stage disease, monotherapy) in USA (PO) Updated 06 Dec 2012
30 Nov 2007	Phase Change - II	Phase-II clinical trials in Biliary cancer in USA (PO) Updated 15 May 2008
09 Aug 2007	Phase Change - II	Phase-II clinical trials in metastatic Colorectal cancer (second- or third-line therapy) in Brazil (PO) Updated 26 Nov 2007
31 Jan 2007	Phase Change - II	Phase-II clinical trials in Thyroid cancer (Monotherapy) in Canada (PO) Updated 22 Jun 2015
31 Jan 2007	Phase Change - II	Phase-II clinical trials in Thyroid cancer in USA (PO) Updated 15 May 2008
08 Dec 2006	Scientific Update	Data presented at the 18th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR 2006) added to the adverse events, pharmacokinetic, pharmacodynamic and Cancer therapeutic trials sections [31], [32] Updated 08 Dec 2006
14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Pancreatic cancer (second-line therapy) in Australia (PO) Updated 15 Feb 2011

14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Pancreatic cancer (second-line therapy) in Bulgaria (PO) Updated 15 Feb 2011
14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Pancreatic cancer (second-line therapy) in Hungary (PO) Updated 15 Feb 2011
14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage Non-small cell lung cancer (second- or third-line therapy) in Romania (PO) Updated 26 Nov 2007
14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage Non-small cell lung cancer (second- or third-line therapy) in Bulgaria (PO) Updated 26 Nov 2007
14 Nov 2006	Phase Change - II	Phase-II clinical trials in late-stage or metastatic Pancreatic cancer (second-line therapy) in USA (PO) Updated 28 Dec 2006
08 Jun 2006	Phase Change - II	Phase-II clinical trials in late-stage Malignant melanoma (first-line monotherapy) worldwide (PO) Updated 12 Jun 2006
07 Dec 2005	Scientific Update	Data presented at the 17th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2005) have been added to the adverse events [107], pharmacokinetics [107], pharmacodynamics [108] and Cancer therapeutic trials sections [107] Updated 07 Dec 2005
18 Jun 2004	Phase Change - I	Phase-I clinical trials in Cancer (Combination therapy, late-stage disease, second-line or greater therapy) in USA (PO) Updated 18 Jun 2004
16 Apr 2004	Scientific Update	Data presented at the 95th Annual Meeting of the American Association for Cancer Research (AACR-2004) have been added to the Cancer pharmacodynamics section [109], [110], [111], [112] Updated 16 Apr 2004
10 Mar 2004	Regulatory Status	Array BioPharma has received approval from the FDA for a phase I clinical study in cancer Updated 10 Mar 2004
08 Jan 2004	Licensing Status	ARRY 142886 and certain second-generation anticancer compounds have been licensed to AstraZeneca worldwide Updated 08 Jan 2004
26 Aug 2003	Phase Change - Preclinical	Preclinical trials in Cancer in USA (PO) Updated 26 Aug 2003

References

1. AstraZeneca collaborates with Cambridge medical research institutions to advance cancer research.

   Media Release

2. AstraZeneca and Merck & Co., Inc. Form Pioneering Collaboration to Investigate Novel Combination Anticancer Regimen.

   Media Release

3. Array BioPharma and AstraZeneca Announce Oncology Collaboration.

   Media Release

4. Array BioPharma Reports Financial Results for the Third Quarter of Fiscal 2008.

   Media Release

5. A Phase 2 Study of AZD6244 in Relapsed or Refractory AML

   ctiprofile

6. Odenike O, Curran E, Iyengar N, Popplewell L, Kirschbaum M, Erba HP, et al. Phase II study of the oral MEK inhibitor AZD6244 in advanced acute myeloid leukemia. 51st-ASH-2009 2009; abstr. 2081.

   Available from: URL: ***http://www.hematology.org***

7. A Phase II Randomized Multicenter Open Label Prospective Study of Neoadjuvant Chemotherapy Docetaxel With or Without MEK Inhibitor SELUMETINIB in Patients With Early and Locally Advanced Triple Negative Breast Cancer

   ctiprofile

8. A Randomized Phase II Trial of MEK Inhibitor Selumetinib (AZD6244) Combined Continuously or Sequentially With Cisplatin/Gemcitabine (CIS/GEM) Versus CIS/GEM Alone in Patients With Advanced Biliary Cancer

   ctiprofile

9. A Phase 2 Study of AZD6244 in Biliary Cancers.

   ctiprofile

10. A Phase I, Open-Label, Multi-center Study to Assess the Safety and Tolerability of AZD6244 (Selumetinib, ARRY142886) in Combination With Cisplatin/Gemcitabine in Japanese Patients With Inoperable Locally Advanced or Metastatic Biliary Tract Cancer (BTC)

    ctiprofile

11. Selecting cancer patients for treatment using Tumor Organoids, the SENSOR study.

    ctiprofile

12. A Dose Finding and Phase II Study of Selumetinib (AZD6244) (Hyd-Sulfate) in Combination With Irinotecan, in 2nd Line Patients With K-ras or B-raf Mutation Positive Advanced or Metastatic Colorectal Cancer.

    ctiprofile

13. Capasso A, Dasari A, Lockhart AC, Stein M, Sanoff H, Lee J, et al. A phase IB study of the combination of AZD6244 hydrogen sulfate (selumetinib) and cyclosporin A (CsA) in patients with advanced solid tumors with an expansion cohort in metastatic colorectal cancer (mCRC). AACR-2016 2016; abstr. CT146.

    Available from: URL: ***http://www.abstractsonline.com/plan/AbstractPrintView.aspx?mID=4017&sKey=52d974f0-19a8-42ac-86d9-2d23e27327c8&cKey=f7710034-2a1f-411c-80fd-7d1d33f8da42&mkey=%7b1D10D749-4B6A-4AB3-BCD4-F80FB1922267%7d***

14. A Phase IB Study of the Combination of AZD6244 Hydrogen Sulfate (Selumetinib) and Cyclosporin A (CsA) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Colorectal Cancer

    ctiprofile

15. A Phase II, Open, Randomized Study to Assess the Efficacy and Safety of AZD6244 vs Capecitabine (Xeloda) in Patients With Colorectal Cancer Who Have Failed One or Two Prior Chemotherapeutic Regimens.

    ctiprofile

16. Lang I, Adenis A, Boer K, Escudero P, Kim T, Valladares M, et al. AZD6244 (ARRY-142886) versus capecitabine in patients with metastatic colorectal cancer who have failed prior chemotherapy. 44th-Ann-Meet-Am-Soc-Clin-Oncol 2008; abstr. 4114.

    Available from: URL: ***http://www.asco.org***

17. Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma

    ctiprofile

18. AstraZeneca Announces Innovative New Partnership With Singapore Institutions to Develop Anti-Cancer Compounds.

    Media Release

19. A Phase 1/2 Study of AZD6244 in Combination With Sorafenib in Advanced Hepatocellular Carcinoma

    ctiprofile

20. A Phase 2 Study of AZD6244 in Advanced or Metastatic Hepatocellular Carcinoma.

    ctiprofile

21. Array BioPharma Reports Financial Results for the Third Quarter of Fiscal 2013.

    Media Release

22. Array BioPharma Reports Financial Results for the First Quarter of Fiscal 2012.

    Media Release

23. Array BioPharma and AstraZeneca Announce New Phase 2 Development Plans for the Investigational Anti-Cancer Drug AZD6244 (ARRY-886).

    Media Release

24. Array BioPharma Reports Financial Results for the Fourth Quarter and Full Year of Fiscal 2008.

    Media Release

25. A Phase II, Double-Blind, Randomised Study to Assess the Efficacy of AZD6244 in Combination With Dacarbazine Compared With Dacarbazine Alone in First Line Patients With BRAF Mutation Positive Advanced Cutaneous or Unknown Primary Melanoma

    ctiprofile

26. A Phase II, Multi-centre, Open-Label, Parallel Group, Randomised Study To Compare the Efficacy of AZD6244 vs Temozolomide in Patients With Unresectable AJCC Stage 3 or 4 Malignant Melanoma.

    ctiprofile

27. Topline Results Announced from a Phase 2 Study in Advanced Melonoma of Investigational Anti-Cancer Drug AZD6244 (ARRY-886).

    Media Release

28. Array BioPharma Reports Financial Results for the Fourth Quarter and Full Year of Fiscal 2006.

    Media Release

29. AstraZeneca and Array BioPharma Announce Initiation of Phase II Studies for AZD6244 (ARRY-142886).

    Media Release

30. Two Array Invented MEK Inhibitors Showcased At ASCO.

    Media Release

31. Enzyme inhibitor produces stable disease in patients with advanced solid cell cancers: phase II trials initiated.

    Media Release

32. Adjei A, Cohen RB, Franklin WA, Molina J, Hariharan S, Temmer E, et al. Phase 1b and pharmacodynamic study of the MEK inhibitor AZD6244 (ARRY-142886) in patients with advanced solid malignancies. EJC-Suppl 2006;4(12):12 (plus oral presentation) abstr. 26.
33. A Phase 2 Study of AZD6244 in Multiple Myeloma.

    ctiprofile
34. ASTRAZENECA UPDATE ON SELUMETINIB PHASE III TRIAL.

    Media Release
35. AstraZeneca PLCAnnounces Q1 2016 Results.

    Media Release
36. Array BioPharma Reports Financial Results for the Third Quarter of Fiscal 2014.

    Media Release
37. Array BioPharma Reports Financial Results For The First Quarter Of Fiscal 2015.

    Media Release
38. Array BioPharma Reports Financial Results For The Fourth Quarter And Full Year Of Fiscal 2014.

    Media Release
39. AstraZeneca Provides Update On Phase III Trial Of Selumetinib In Non-Small Cell Lung Cancer.

    Media Release
40. Janne PA, van den Heuvel M, Barlesi F, Cobo M, Mazieres J, Crino L, et al. Selumetinib in combination with docetaxel as second-line treatment for patients with KRAS-mutant advanced NSCLC: Results from the phase III SELECT-1 trial. ESMO-2016 2016; abstr. N/A.

    Available from: URL: ***http://annonc.oxfordjournals.org/content/27/suppl_6/LBA47_PR.full?sid=98a516b3-fda7-4630-9d8b-0696f30933cc***
41. Array BioPharma Reports Financial Results For The Second Quarter Of Fiscal 2013.

    Media Release
42. AstraZeneca initiates phase III clinical programme for selumetinib, a treatment in development for patients with advanced or metastastic non-small-cell lung cancer.

    Media Release
43. A Phase III, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination With Docetaxel, in Patients Receiving Second Line Treatment for KRAS Mutation-Positive Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB - IV) (SELECT 1)

    ctiprofile
44. AstraZeneca Initiates Phase 3 Clinical Trial For Selumetinib In Non-Small Cell Lung Cancer.

    Media Release
45. Array BioPharma Reports Financial Results For The Third Quarter Of Fiscal 2016.

    Media Release
46. Phase II Trial of Immunotherapy With Durvalumab (MEDI4736) With Continuous or Intermittent MEK Inhibitor Selumetinib in KRAS Mutant Non-Small Cell Lung Cancer (NSCLC)

    ctiprofile
47. A Randomized, Open-Label, Phase I Trial of Continuous, Intermittent, and Pulsatile Selumetinib (AZD6244) Plus Paclitaxel as Second-Line Treatment for Stage IIIB or IV Non-small Cell Lung Cancer (NSCLC)

    ctiprofile
48. A Phase IIa, Open-Label, Multi-Center, Multi-Cohort, Immune-Modulated Study of Selected Small Molecules (Gefitinib, AZD9291, or Selumetinib + Docetaxel) or a 1st Immune-Mediated Therapy (IMT; Tremelimumab) With a Sequential Switch to a 2nd IMT (MEDI4736) in Patients With Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (Stage IIIB-IV)

    ctiprofile

49. Promising Data for KRAS Mutant Advanced NSCLC Patients Presented at ASCO.

    Media Release

50. Topline Results: A Randomized Phase 2 Study of Selumetinib in Patients with KRAS-Mutant Non-Small Cell Lung Cancer.

    Media Release

51. A Phase II, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy and Safety of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Combination with Docetaxel, Compared with Placebo in Combination with Docetaxel, in Patients receiving second line treatment for Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB – IV)

    ctiprofile

52. Randomized Phase II Study of AZD6244 MEK-Inhibitor With Erlotinib in KRAS Wild Type and KRAS Mutant Advanced Non-Small Cell Lung Cancer.

    ctiprofile

53. A Phase II, Open, Randomised Study to Assess the Efficacy and Safety of AZD6244 Versus Pemetrexed (Alimta) in Patients With Non-small Cell Lung Cancer, Who Have Failed One or Two Prior Chemotherapy Regimen

    ctiprofile

54. Tzekova V, Cebotaru C, Ciuleanu TE, Damjanov D, Ganchev H, Kanarev V, et al. Efficacy and safety of AZD6244 (ARRY-142886) as second/third-line treatment of patients with advanced non-small cell lung cancer. 44th-Ann-Meet-Am-Soc-Clin-Oncol 2008; abstr. 8029.

    Available from: URL: ***http://www.asco.org***

55. A Randomized Phase II Trial of Selumetinib in Patients Receiving Standard Pemetrexed and Cisplatin Chemotherapy for the Treatment of Advanced or Metastatic KRAS Wildtype or Unknown Non-Squamous Non-Small Cell Lung Cancer

    ctiprofile

56. A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety,Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI (TATTON).

    ctiprofile

57. AstraZeneca Presents Positive Data on AZD9291 in First-Line EGFR Mutated Lung Cancer at ASCO 2015.

    Media Release

58. Dean E, Steele N, Arkenau H-T, Blackhall F, Haris NM, Lindsay C, et al. SELECT-3: A phase I study of selumetinib in combination with platinum doublet chemotherapy for advanced NSCLC in the first-line setting. ESMO-2016 2016; abstr. N/A.

    Available from: URL: ***http://annonc.oxfordjournals.org/content/27/suppl_6/1269P.full?sid=539d5a67-8497-4f7b-a44f-74a84ee3edd2***

59. A Phase I, Open Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Selumetinib (AZD6244; ARRY-142886) in Combination With First Line Chemotherapy Regimens in Patients With Non-Small Cell Lung Cancer (NSCLC)

    ctiprofile

60. A Phase Ib Study of Selumetinib in Patients with Previously Treated or Untreated Advanced/Metastatic NSCLC Who are Receiving Standard Chemotherapy Regimens

    ctiprofile

61. A Phase I, Open-Label Study to Investigate the Safety and Tolerability of AZD6244 (Selumetinib) When Given as a Monotherapy in Japanese Patients With Advanced Solid Malignancies, and When Given in Combination With Docetaxel as 2nd Line Therapy in Japanese Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV)

    ctiprofile

62. Array BioPharma Reports Financial Results For The Fourth Quarter And Full Year Of Fiscal 2016.

    Media Release

63. Phase II Trial of the MEK1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas

    ctiprofile

64. Two Array-Invented MEK Inhibitors Showcased At ASCO 2 June 2014.

    Media Release

65. A Phase 1/2 Study of the Mitogen Activated Protein Kinase Kinase(MEK) 1 Inhibitor Selumetinib (AZD6244, Hydrogen Sulfate) in Children With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)

    ctiprofile

66. Array BioPharma Reports Financial Results For The Third Quarter Of Fiscal 2015.

    Media Release

67. Pilot Study of the MEK1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) for Adults With Neurofibromatosis Type 1(NF1) and Dermal Neurofibromas (DN)

    ctiprofile

68. A phase II, open, randomised study to assess the efficacy and safety of AZD6244 vs. capecitabine (Xeloda[Rm]) in patients with advanced or metastatic pancreatic cancer, who have failed first line gemcitabine therapy

    ctiprofile

69. A Phase II Study of Selumetinib (AZD6244) for the Treatment of Advanced Pancreas Cancer Harboring KRAS G12R Mutations

    ctiprofile

70. A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients With Differentiated Thyroid Cancer

    ctiprofile

71. Phase 2 Study of Selumetinib Hydrogen Sulfate in Iodine-131 Refractory Papillary Thyroid Carcinoma and Papillary Thyroid Carcinoma With Follicular Elements

    ctiprofile

72. Randomized Double-Blind Phase II Study of Radioactive Iodine (RAI) in Combination With Placebo or Selumetinib for the Treatment of RAI-Avid Recurrent/Metastatic Thyroid Cancers

    ctiprofile

73. Investigating the potential clinical benefit of Selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy.

    ctiprofile

74. Reacquisition of RAI Uptake of RAI-Refractory Metastatic Thyroid Cancers by Pretreatment With the Selective MEK Inhibitor AZD6244: A Pilot Study.

    ctiprofile

75. Selumetinib granted Orphan Drug Designation in the US for adjuvant treatment of differentiated thyroid cancer.

    Media Release

76. AstraZeneca Provides Update On Selumetinib In Uveal Melanoma.

    Media Release

77. Array BioPharma Announces Clinical Data Presentations At The 2015 ASCO Annual Meeting.

    Media Release

78. Array BioPharma Reports Financial Results For The First Quarter Of Fiscal 2014 And Announces ARRY-520 Development Strategy.

    Media Release

79. A Randomised, Double-Blind Study to Assess the Efficacy of Selumetinib (AZD6244: ARRY-142886) (Hyd-Sulfate) in Combination With Dacarbazine Compared With Placebo in Combination With Dacarbazine as First Systemic Therapy in Patients With Metastatic Uveal Melanoma (SUMIT)

    ctiprofile

80. A Randomised three arm, open-label, Phase II study of continuous Selumetinib versus continuous or interrupted Selumetinib in combination with weekly Paclitaxel in metastatic Uveal Melanoma

    ctiprofile

81. Selumetinib granted Orphan Drug Designation by US FDA for treatment of uveal melanoma.

    Media Release

82. A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of Selumetinib (AZD6244 Hyd-sulfate) in Combination With MEDI4736 in Patients With Advanced Solid Tumours

    ctiprofile

83. A Phase I, Open-Label, Multi-Center Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD6244 Hyd-Sulfate When Given in Combination with Standard Doses of Selected Chemotherapies to Patients with Advanced Solid Tumors

    ctiprofile

84. Kim K, Infante J, Cohen R, Burris H, Emeribe U, Curt G, et al. A Phase I dose-escalation study of selumetinib in combination with docetaxel in patients with advanced solid tumors. 23rd-AACR-NCI-EORTC-2011 2011; abstr. B225.

    Available from: URL: ***http://www.abstractsonline.com/plan/viewabstract.aspx?mid=2889&skey=e4a7499b-850c-46e7-a71d-753261881cd1&ckey=f9b16c89-b5bc-4182-aa4e-2b3e6d2d644c&mkey=%7ba57ff86d-d414-4079-bcbd-157746574f37%7d***

85. A Phase I Study of Oral MK2206 in Combination With Oral AZD6244 in Patients With Locally Advanced or Metastatic Solid Tumors

    ctiprofile

86. First Patient Enrolled in Phase I Clinical Trial of Landmark AstraZeneca, Merck & Co. Novel Combination Anticancer Regimen.

    Media Release

87. A Phase I, Single Centre, Randomised, Open Label, Crossover Study to Assess the Bioequivalence or Relative Bioavailability of Variants of Selumetinib (AZD6244, Hyd-Sulfate) Blue Capsules in Healthy Male Volunteers Aged 18 to 45 Years

    ctiprofile

88. A Phase II Trial of AZD6244 (NSC 748727) in Women With Recurrent Low-Grade Serous Carcinoma of the Ovary or Peritoneum

    ctiprofile

89. Array BioPharma Reports Financial Results for the Third Quarter of Fiscal 2012.

    Media Release

90. A Study to Assess the Absolute Bioavailability of a Single Oral Dose of Selumetinib With Respect to an Intravenous Microdose of [14C] Selumetinib in Healthy Male Volunteers

    ctiprofile

91. A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 Inducer Rifampicin on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers Aged 18 to 45 Years

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92. A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [14C]-Selumetinib in Healthy Male Volunteers

    ctiprofile

93. A Phase I, Single-centre, Open-label, Dose-escalation Study to Assess the Safety, Tolerability

and Pharmacokinetics of Selumetinib Given Orally in Japanese and Non-Japanese Asian Healthy Male Volunteers

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94. A Phase I, Single-center, Randomized, Open-label, Crossover Study to Compare the White (Current Phase II) and Blue (Planned Phase III) Capsule Formulations of AZD6244 Hyd-Sulfate in Healthy Male Subjects

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95. A Phase I, Open-label, Single-center Study to Assess the Effect of the CYP3A4 Inhibitor Itraconazole and the CYP2C19 Inhibitor Fluconazole on the Pharmacokinetics of a 25 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142866) (Hyd-Sulfate) in Healthy Volunteers Aged 18 to 45 Years

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96. An Open Label Comparative Study of the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY 142886) (Hyd Sulfate) Following a Single Oral Dose in Subjects With Renal Impairment and Healthy Subjects

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97. An Open-label, Comparative Study to Assess the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) Following Single Oral Dosing to Healthy Subjects and to Subjects With Mild, Moderate, and Severe Hepatic Impairment

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98. A Phase I, Double-blind (Selumetinib [AZD6244; ARRY-142886] [Hyd-Sulfate]), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, Using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male Volunteers Aged 18 to 45 Years

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99. A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Male Volunteers Aged 18 to 45 Years

    ctiprofile

100. Takahashi O, Komaki R, Smith PD, J?rgensmeier JM, Ryan AJ, Bekele BN, et al. MEK inhibition by selumetinib (AZD6244) inhibits progression with a multicentric antiangiogenic effect and enhances the efficacy of cediranib in orthotopic human lung cancer models. 102nd-AACR-2011 2011; abstr. 629.

     Available from: URL: ***http://www.aacr.org***

101. Odedra R, Heaton S, Logie A, Mundt KE, Anderson E, Smith PD, et al. Combined targeting of Aurora B (AZD1152) and MEK1/2 (AZD6244) kinases leads to enhancement of anti-tumour effects in vivo. 101st-AACR-2010 2010; abstr. 4434.

     Available from: URL: ***http://www.abstractsonline.com***

102. Bekaii-Saab T, Phelps M, Li X, Saji M, Kosuri K, Goff L, et al. A multi-institutional study of AZD6244 (ARRY-142886) in patients with advanced biliary cancers. 100th-AACR-2009 2009;(Late Breaking Abstr.)42 abstr. LB-129.

     Available from: URL: ***http://www.aacr.org***

103. Morelli MP, Meyer AM, Tentler JJ, Pitts TM, Nallapareddy S, Smith PD, et al. Vorinostat sensitizes colorectal cancer cell (CRC) lines to AZD6244 and results in synergistic inhibitory effects on proliferation. 20th-EORTC-NCI-AACR-2008 2008;111 abstr. 349.

     Available from: URL: ***http://www.ecco-org.eu***

104. Desar I, Gilles R, Timmer-Bonte A, Cantarini MV, Van Herpen CML, Oyen WJG, et al. 18F-FLT-PET for the evaluation of MEK inhibitor AZD6244. 20th-EORTC-NCI-AACR-2008 2008;113 abstr. 358.

     Available from: URL: ***http://www.ecco-org.eu***

105. Sarker D, Banerji U, Agarwal R, Camidge DR, Verheul HMW, Brown KH, et al. Relative oral bioavailability of the hydrogen sulphate capsule and free base suspension formulations of

AZD6244 (ARRY-142886): a phase I trial in patients with advanced cancer. 33rd-ESMO 2008; abstr. 492P.

Available from: URL: ***http://annonc.oxfordjournals.org***

106. Dummer R, Robert C, Chapman PB, Sosman JA, Middleton M, Bastholt L, et al. AZD6244 (ARRY-142886) vs temozolomide in patients with advanced melanoma: an open-label, randomized, multicenter, phase II study. 44th-Ann-Meet-Am-Soc-Clin-Oncol 2008; (plus poster) abstr. 9033.

    Available from: URL: ***http://www.asco.org***

107. Chow LQM, Eckhardt SG, Reid J, Molina J, Hanson L, Piens J, et al. A first in human dose-ranging study to assess the pharmacokinetics, pharmacodynamics, and toxicities of the MEK inhibitor, ARRY-142886 (AZD6244), in patients with advanced solid malignancies. 17th-AACR-NCI-EORTC 2005;239 (plus poster) abstr. C162.
108. Cockerill M, Logie A, Speake G, Beck S, Cartlidge S, Smith PD, et al. Combination studies in vitro and in vivo with gefitinib (Iressa) and the MEK1/2 inhibitor AZD6244 (ARY142886). 17th-AACR-NCI-EORTC 2005;83 (plus poster) abstr. A110.
109. Lyssikatos J, Yeh T, Wallace E, Marsh V, Bernat B, et al. ARRY-142886, a potent and selective MEK inhibitor: I. ATP-independent inhibition results in high enzymatic and cellular selectivity. 95th-AACR 2004;45896.
110. Yeh T, Wallace E, Lyssikatos J, Winkler J. ARRY-142886, a potent and selective MEK inhibitor: II. Potency against cellular MEK leads to inhibition of cellular proliferation and induction of apoptosis in cell lines with mutant Ras or B-Raf. 95th-AACR 2004;45896-897.
111. Lee P, Wallace E, Yeh T, Poch G, Litwiler K, et al. ARRY-142886, a potent and selective MEK inhibitor: III. Efficacy in murine xenograft models correlates with decreased ERK phosphorylation. 95th-AACR 2004;45897.
112. Wallace E, Yeh T, Lyssikatos J, Winkler J, Lee P, et al. Precliical development of ARRY-142886, a potent and selective MEK inhibitor. 95th-AACR 2004;45897.
113. Holt SV, Logie A, Davies BR, Cockerhill M, Haupt N, Curtis NJ, et al. A MEK1/2 inhibitor, AZD6244 (ARRY-142886), shows beneficial effects when combined with standards of care or novel therapies - mechanistic characterisation suggests a role for apoptosis. 20th-EORTC-NCI-AACR-2008 2008;86 abstr. 265.

    Available from: URL: ***http://www.ecco-org.eu***

114. Array BioPharma Reports Financial Results For The Second Quarter Of Fiscal 2017.

    Media Release

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